Clinical Trial Protocol

Document Number:		**c03063854-14**
EudraCT No.:	2015-001111-12	
BI Trial No.:	1367.1	
BI Investigational Product(s):	BI 894999	
Title:	An open label, Phase Ia/Ib dose finding study with BI 894999 orally administered once a day in patients with advanced malignancies with repeated administration in patients with clinical benefit	
Brief Title:	BI 894999 first in human dose finding study in advanced malignancies	
Clinical Phase:	Phase Ia/Ib	
Trial Clinical Monitor:	[redacted] Phone: Fax:	
Coordinating Investigator:	[redacted] Phone: Fax:	
Status:	**Final Protocol (Revised Protocol based on global amendment 11)**	
Version and Date:	**Version: 12.0**	**Date: 24 Jun 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product: NA			
Name of active ingredient:		BI 894999	
Protocol date: 30 Mar 2015	**Trial number:** 1367.1		**Revision date:** **24 Jun 2020**

Title of trial:	An open label, Phase Ia/Ib dose finding study with BI 894999 orally administered once a day in patients with advanced malignancies, with repeated administration in patients with clinical benefit
Coordinating Investigator:	[redacted] Phone: [redacted] Fax: [redacted]
Trial site(s):	Multi-centre trial in 1 up to 10 countries
Clinical phase:	Phase Ia/Ib
Objective(s):	<u>Dose escalation part (Phase Ia)</u> To investigate the maximum tolerated dose (MTD) through dose limiting toxicities (DLTs), safety and tolerability, pharmacokinetics, f[redacted] biomarker and efficacy of BI 894999 monotherapy in patients with advanced and/or metastatic solid tumours in three different schedules (Schedule A with continuous dosing, Schedule B with two weeks on treatment and one week off in 3-week cycles, Schedule C with a loading dose on Day 1 followed by a maintenance dose on the six next days and a week off, repeated every two weeks in 4-week cycles) and provide safety data in terms of drug-related adverse events (AEs) for the recommendation of the dose and schedule of treatment for the expansion Phase Ib of this trial (between Schedules A and B) and for further trials in the development of BI 894999 (between Schedules B and C). To determine the MTD in patients with diffuse large B-cell lymphoma (DLBCL) once the MTD has been determined for both schedules A and B in patients with solid tumours, (Schedule B was selected based on Schedule A and B data according to the Data Monitoring Committee (DMC) recommendation). The MTD will also be determined for Schedule C in DLBCL patients. Once both MTDs for Schedule B and Schedule C are determined for DLBCL, the DMC will recommend the best schedule and dose to be used for the extension of MTD cohort in DLBCL patients. <u>Expansion part (Phase Ib)</u> To further collect safety information, PK and anti-tumour activity at the recommended dose and schedule in patients with solid tumours to confirm the RP2D

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	and schedule.
Methodology:	Uncontrolled, open label, dose escalation followed by an expansion cohort phase
No. of patients:	Up to approximately 204
total entered:	<u>Dose escalation part (Phase Ia): approximately 104 patients</u> - a number of 40 patients (actual number was 40) for determination of MTD in both Schedules A and B in solid tumours, - an extension of MTD cohort in solid tumours with 6 patients (actual number was 7) with the selected schedule by DMC (which was Schedule B) in order to have 12 patients treated at MTD and evaluable for DLT, - approximately 12 patients (actual number was 16) to determine the MTD in Schedule C in solid tumours patients - 7 additional patients to confirm the MTD in Schedule C in solid tumours patients in order to have 12 patients treated at MTD - approximately 12 patients (actual number was 14) to determine the MTD with Schedule B in the DLBCL cohort - approximately 12 patients to determine the MTD with Schedule C in the DLBCL cohort - 6 up to 8 additional patients in the extension of MTD in the DLBCL cohort with Schedule B or Schedule C, according to the DMC recommendation on the best schedule between B and C <u>Expansion part (Phase Ib): approximately 80 up to 100 patients</u> - 9 to 20 for each of the three types of solid tumour in the expansion part with Schedule B according to the decision taken by the DMC: SCLC, mCRPC and CRC 37 patients were recruited in the three cohorts. Cohorts of colorectal cancer (CRC), small cell lung cancer (SCLC)and metastatic castrate resistant prostate cancer (mCRPC) were closed for futility after 9 evaluable patients per RECIST 1.1 or Prostate Cancer Clinical Trials Working Group 3 (PCWG3) - 20 patients for the NUT carcinoma (NC) cohort were recruited with Schedule B. Up to 40 patients to be recruited with Schedule C which was opened after the DMC decision to open the NC cohort with Schedule C and to close the NC cohort with Schedule B
each treatment:	Up to 204
Diagnosis :	Patients with a confirmed diagnosis of an advanced and/or metastatic solid tumour or relapsed/refractory DLBCL

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Main criteria for inclusion:	In the dose escalation phase: adult patients with a confirmed diagnosis of advanced, unresectable and/or metastatic malignant solid tumour or relapsed/refractory DLBCL, and who have failed conventional treatment or for whom no therapy of proven efficacy exists or who are not amenable to standard therapies. In the expansion phase: recruitment is restricted to the following solid tumours types: SCLC, mCRPC, CRC and NC. Age ≥ legal adult age in the given country (except for NC, where patients ≥ 15 years of age at the time of consent may be included in countries where allowed).
Test product(s):	BI 894999
dose:	Starting dose was 0.2 mg once per day for the very first patient of the trial, treated in Schedule A
mode of administration:	Once daily oral intake, in three different schedules: - Schedule A: continuous dosing schedule, repeated every 3 weeks - Schedule B: two weeks on treatment, one week off treatment, repeated every 3 weeks - Schedule C: loading dose on Day 1 followed by a maintenance dose on the six next days and a week off, repeated every two weeks in 4-week cycles
Comparator products:	NA
dose:	NA
mode of administration:	NA
Duration of treatment:	One treatment cycle consists of 21 days in Schedules A and B and of 28 days in Schedule C. Minimum of one treatment cycle, continued until disease progression or intolerability of the trial drug.
Endpoints	**Dose escalation part (Phase Ia) in patients with solid tumours and in patients with DLBCL:** <u>Primary:</u> - Number of patients experiencing DLT graded according to the common terminology criteria for adverse events (CTCAE) v. 4.03, observed in the first cycle (3 weeks for Schedules A and B, 4 weeks for Schedule C) in order to meet the objective of assessment of the MTD of BI 894999 for each schedule in patients with solid tumours and for Schedules B and C in the DLBCL cohort <u>Secondary:</u> - C_{max} and AUC_{0-24} after single and $C_{max,ss}$ and $AUC_{\tau,ss}$ after multiple dose of

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BI 894999, as measured during the first cycle (3 weeks for Schedules A and B, 4 weeks for Schedule C)

- Number of patients experiencing DLTs from start of treatment until end of treatment (in all cycles) as assessed approximately every 3 weeks for Schedules A and B, 4 weeks for Schedule C after Cycle 2, for each schedule in patients with solid tumours and for Schedules B and C in the DLBCL cohort
- Objective Response (Complete Response (CR) and Partial Response (PR)) according to RECIST version 1.1 as assessed by the investigator throughout the entire treatment period for each schedule in patients with solid tumours and according to RECIL 2017 for the Schedules B and C in the DLBCL cohort (a minor response is not included as a PR for RECIL 2017 evaluation)

Expansion part (Phase Ib) in patients with solid tumours:

Primary:

- Number of patients experiencing DLTs from start of treatment until end of treatment (in all cycles) as assessed approximately every 3 weeks for Schedule B (at the end of each new cycle) in order to determine the recommended Phase II dose with the schedule selected at the end of Phase Ia, schedules A and B part. Schedule B was selected.

If the DMC decides that the safety profile of Schedule C is better than Schedule B in Phase Ia solid tumours, the following endpoint will be assessed:

- Number of NC patients in the Schedule C cohort experiencing DLTs from start of treatment until end of treatment (in all cycles) as assessed every 4 weeks.

  For the NC cohort, a comparison of safety profile will be performed at the end of the trial, if applicable, in order to determine the recommended Phase II schedule and dose

Secondary:

- C_{max} and AUC_{0-24} after single and $C_{max,ss}$ and $AUC_{\tau,ss}$ after multiple dose of BI 894999, observed in the first 3 weeks for Schedule B (first cycle) or in the first 4 weeks for Schedule C NC cohort (first cycle)
- Objective response (CR, PR) as assessed by the investigator with a tumour assessment by RECIST 1.1 every 2 cycles (6 weeks if no delays for Schedule B, 8 weeks for the NC cohort with Schedule C) during the entire treatment period. For mCRPC patients with non-measurable disease by RECIST 1.1, the assessment will be performed by bone scan plus prostate specific antigen (PSA) percentage change at the same time-points as bone

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	scan every 4 cycles (12 weeks if no delays for Schedule B), as described by the PCWG3 - Progression-free Survival (PFS) with tumour assessment every 2 cycles (6 weeks if no delays for Schedule B, 8 weeks for the NC cohort with Schedule C) during the treatment period and until progression or death is reported (radiological PFS with tumour assessment by bone scan every four cycles for mCRPC patients with non-measurable disease by RECIST 1.1) - Best overall response with an evaluation of approximately every 2 cycles (6 weeks if no delays for Schedule B, 8 weeks for the NC cohort with Schedule C) during the entire treatment period (every four cycles for mCRPC patients with non-measurable disease by RECIST 1.1) - In mCRPC patients: PSA response – defined as a decline in PSA value ≥ 50% with an evaluation every cycle during the entire treatment period - Overall survival (OS) for the NC patients
Safety criteria:	Adverse events (AE) according to CTCAE v. 4.03, incidence of DLTs, determination of MTD, laboratory evaluations, vital signs, electrocardiograms (ECG), left ventricular ejection fraction (LVEF).
Statistical methods:	For the primary endpoint in the Phase Ia part of this study, a Bayesian logistic regression model (BLRM) with overdose control will be fitted to binary toxicity outcomes. The estimate of parameters will be updated as data are accumulated using the BLRM. At the end of the Phase Ia part for Schedules A and B, the toxicity probability at each dose level was calculated to determine the MTD. The analysis of the primary endpoint of the Phase Ia part happened once the last entered patient with solid tumour from Schedules A and B reached Day 22 of the first cycle and was evaluable for DLT occurrence or not in the first cycle. Results of the primary endpoint of the Phase Ia part in patients with solid tumours for Schedule C and for DLBCL patients in Schedules B and C are planned to be reported with final analysis of the trial. For the primary endpoint in the Phase Ib part of this study, the number of patients with DLT during the entire treatment period will be summarized by cohorts. The analysis of the primary endpoint of the Phase Ib part will happen together with the final analysis when the last ongoing patient will have reached 4 cycles of trial treatment or stopped trial treatment and will have performed the end of residual effect period (EOR) visit, at least 30 days after last trial drug intake, whatever occurs first. An updated report will then be written once the last ongoing patients will have reached the end of trial. Exploratory analyses and descriptive statistics will be used for secondary endpoints

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	of toxicity, pharmacokinetics (PK) parameters, and efficacy. [redacted] For the Phase Ib part, a 2-stage Bayesian hierarchical model approach will be implemented with an interim futility assessment conducted when approximate 9 patients are enrolled and treated in each of the SCLC, mCRPC and CRC patients' cohorts. If no objective response is observed in the 9 first patients evaluable for efficacy in a cohort with Schedule B, then this cohort will be closed for the stage 2 of the phase Ib part. For the response endpoints (i.e. objective response, disease control) in the Phase Ib part, a Bayesian hierarchical modelling approach with a scale parameter for the inter-cohort variability will be used. The prior for the inter-cohort variability will be chosen as half-normal with a scale parameter of 100. Thereby the shrinkage estimators allowing borrowing information from different patient cohorts will be considered (response data from the MTD expansion cohort of DLBCL will also be considered in the Bayesian hierarchical model). Additionally descriptive statistics of these endpoints for the specific cohorts will be provided.		

FLOW CHART FIRST TREATMENT CYCLE IN SCHEDULE A*

Study Periods	**Screen**	**Treatment Cycle 1**								**EOT**[1]	**FU**[2]
Visit	**Screen**	**1**			**2**	**3**	**4**		**5**[3]	**EOT**	**FU**
Day (day range)	**-28 - 1**	**1**	**2**	**3**[4]	**8 (± 1)**	**12 (± 1)**	**14**	**15**	**22**		**First = EOR +30 (+7) after EOT**
Informed Consents[5]	x										
Demographics	x										
Medical History	x										
In- /Exclusion Criteria	x	x									
Physical Examination	x[22]	x[22]								x[22]	x[6]
Height	x										
Body weight	x	x								x	x
ECOG performance score	x	x								x	x
Pregnancy test	x[7]									x	
12-lead-ECG	x[8]	x[8]	x[8]		x[8]		x[8]	x[8]	x[8]	x[8]	x[6]
LVEF[9]	x									x[23]	x[6]
Dispensing of BI 894999		**x**									
Intake of BI 894999		**x**[10]	**x**[10]	**x**[10]	**x**[10]	**x**[10]	**x**[10]	**x**[10]	**x**[10]		
Compliance check					x	x	x		x	x	
Completion of diary card[11]		x---	----	----	-----	-----	-----	----	---x		
Vital Signs	x	x[12]	x	x	x	x	x[12]	x	x	x	
Safety lab parameters	x[13]	x[13]	x[13]		x		x[13]		x	x[13]	x[6]
Tumour markers[14]	x										
Urine examination[15]	x	x	x				x		x	x	
Pharmacokinetics (plasma)		x[16]	x[16]	x[16]	x[16]	x[16]	x[16]	x[16]			
Pharmacokinetics (urine) [17]		x[17]	x[17]				x[17]	x[17]			
Adverse Events	x	x	x	x	x	x	x	x	x	x	x[18]
Concomitant Therapy	x	x	x	x	x	x	x	x	x	x	x[18]
CT and/or MRI – PET/CT for DLBCL[19]	x[19]									x[19]	x[6]
Bone marrow in DLBCL if PET/CT neg.	x[19]										
Bone scan in mCRPC	x										
Tumour assessment[19]	x									x[19]	x[6]
Tumour biopsy for exploratory [redacted] analysis[20]	x[20]						x[20]				
Mandatory DNA blood[20]							x[20]				
[redacted]		[redacted]					[redacted]				
Optional bio-banking sample		x									
Termination of study medication										x	
Patient's status (alive/PD/dead)											x

[*] Schedule A Flow Chart not updated in this version of the protocol except for the body weight cross at follow-up visit, which was missing in error, since no new patients will be included in this schedule at the time of creation of protocol version 9.0

[1] end of treatment (EOT) investigations which have to be performed at the EOT visit (as soon as possible when a patient discontinues treatment)

[2] FU= follow up visits until progression, lost to follow up, treatment with another anti-cancer drug or end of the whole trial as specified in Section 8.6. The first follow-up visit is the End of Residual Effect Period visit (EOR) which must happen at the earliest 30 days after the end of treatment (see Section 6.2.3.2)

[3] visit 5 of Cycle 1 may correspond to visit 1 of Cycle 2 if an additional cycle is indicated

[4] patients recruited for the food interaction cohorts must have one PK sampling on Day 3 (approximately 24h after BI 894999 intake on Day 2). See Appendix 10.2 for further details

[5] the informed consent consist of 2 forms:

- a main informed consent for participation to the trial including a separate sub-section for participation to the food interaction sub-study and
- a separate informed consent for biomarkers analyses:
    - mandatory blood samples for pharmacogenomics,
    - optional bio-banking sample for pharmacogenomics
    - tumour biopsies for pharmacogenomics biomarkers analyses
        - optional in escalation part until MTD in patients with solid tumours and in DLBCL cohort
        - optional in MTD extension part in patients with solid tumours and in DLBCL cohort
        - mandatory in Phase Ib expansion in patients with solid tumours (at screening and in cycle 1 at steady state)
    - optional consent for sending of archival tissue for genomic analysis in case of objective response or if patient is benefiting from treatment
    - optional consent for a fresh tumour biopsy in patients who have an objective response or are benefiting from treatment
    - mandatory consent for an additional 2-3 mL EDTA Blood DNA tube at the time of objective response or when a patient is benefiting from treatment, if consent is given for archival/fresh tumour biopsy
    - mandatory consent for sampling of an additional 2-3 mL EDTA Blood DNA tube at the time of the fresh tumour biopsy at steady state in cycle 1 for patients who consented to have two fresh tumour biopsies in first cycle

[6] optional, to perform if needed to follow-up on adverse events (AE) present/ongoing at previous visit or if not performed at the EOT visit

[7] a serum or urine beta human chorionic gonadotrophin (βHCG) pregnancy test must be performed within 7 days prior to first treatment in women of childbearing potential

[8] At screening, on Days 1-2 and 14-15: pre-dose and at approximately 2h, 4h, 8h, 24h post-dose, as well as on Days 8 and 22 of Cycle 1 and at EOT. For each ECG, digitalized triplicate acquisition using dedicated equipment for central reading by clinical research organization (CRO). The ECGS are to be performed before the blood sampling when at same time-point as blood sampling (see 5.4.2)

[9] by echocardiography or MUGA scan, but each time by the same method

[10] intake of BI 894999 done at the clinical site on Days 1, 2, 8, 12, 14, 15 and 22 and by the patient anywhere else on the other days

[11] the diary card must be completed every day of intake in Cycle 1

[12] vital signs (blood pressure, pulse and body temperature): on days 1 and 14: pre-dose, and approximately 4h, 8h post-dose. On all other visit days, once at any time during the visit day

[13] including coagulation parameters (aPTT, PT expressed in sec and international normalized ratio (INR)) only to be performed at screening, on Day 1 pre-dose, on Day 2 and pre-dose on the day of tumour biopsy when applicable and at EOT

[14] only in patients with tumour types where there is a clinically relevant tumour marker which is already used in routine clinical practice for tumour restaging (on Day 1 of every cycle). Prostate specific antigen (PSA) mandatory for mCRPC patients

[15] urine examination by dipstick for pH, glucose, erythrocytes, leukocytes, protein, nitrite. If pathological findings, further evaluation (see Section 5.3.3)

[16] intensive PK blood sampling will be performed in Cycle 1, as summarized in Appendix 10.2

For the food interaction cohorts, same PK time points as for other patients with in addition on Day 2: 0:30min, 1h, 2h, 3h, 4h, 6h, 8h 24h (Days 2 and 15) post-dose and on Day 3: 24h post-dose of Day 2 (see 10.2.2).
Pre-dose sampling will be conducted at Days 8 and 12 just before drug administration of the dose

[17] one blank urine will be collected prior to the BI 894999 intake on visit 1 and visit 4 (at least two 2 mL aliquots). In addition urine will be collected as summarized in Appendix 10.2

[18] all AEs and concomitant medication must be collected until 30 days (until EOR) after the last BI 894999 intake. After EOR, for subsequent FU visits, only SAEs/AESIs which are considered study drug related need to be collected as well as their related treatment

[19] according to RECIST 1.1 guidelines for patients with solid tumours (including mCRPC patients who have measurable disease). Imaging and assessment are required every 2 cycles (meaning every 6 weeks if no delays in cycles but as close as possible to the end of the second of the two cycles of treatment if there was a delay).
For mCRPC patients, in addition to the CT/MRI every 2 cycles, a bone scan has to be performed at screening and then every 4 cycles (every 12 weeks if no delays in cycles) with a PSA evaluation at the same time-points as the bone scan.
According to RECIL 2017 guidelines for DLBCL patients, a fluorodeoxyglucose positron emission-tomography (FDG-PET coupled to a computed tomography (CT) scan (or MRI if CT not possible but each time, same method) must be performed at screening, at the end of Cycle 2 (at 6 weeks if no delays in cycles), at the end of Cycle 4 (week 12) and then every 4 cycles. In patients with negative FDG-PET uptake in the bone marrow at screening, a bone marrow aspirate and biopsy need to be performed in order to rule out bone marrow involvement.
EOT/FU imaging and assessment are optional if previous examination was performed in the past 4 weeks

[20] optional for patients in the escalation phase including the patients in the extension of MTD cohort who agree to tumour biopsy, and mandatory for patients in the solid tumour expansion Phase Ib, a tumour biopsy for biomarker analysis (see 5.5.1.2) must be performed at baseline and between Day 11 and Day 14 of Cycle 1: the biopsy may only be performed if the platelet count is above 50 000/mm^3 (coagulation must be checked on the day of the biopsy). For those patients having a tumour biopsy at steady state, a mandatory 2-3 mL EDTA DNA blood sample must be taken at the same time as the tumour biopsy, at steady state. In Phase Ib, for mCRPC patients with only bone metastases and for NC patients, tumour biopsies are not requested.

[21] HEXIM1 (or other genes related to the mechanism of action (MOA) gene expression will be analysed in whole blood as summarized in Appendix 10.2

[22] In DLBCL patients, the physical examination will include a tumour evaluation (largest palpable lymph node per area, measured in two dimensions if one diameter at least is > 1cm, evaluation of spleen and liver enlargement by measuring the cm below costal margin and two dimensional evaluation of any other palpable tumour manifestation).

[23] to be performed if not done in the past 6 weeks and if possible, according to the patient's condition at the time of EOT

FLOW CHART: SECOND AND FURTHER TREATMENT CYCLES IN SCHEDULE A**

Study Periods	**Treatment Cycles**						**EOT**[1]	**FU**[2]
Visit	**C2V1**	**C2V2**	**C2V3**[3]	**CxV1**		**CxV2**[3]	**EOT**	**FU**
Day (day range)	**1**	**15 (-4+2)**	**22**	**1**	**15 (-4+2)***	**22**		**First = EOR +30 (+7) after EOT**
Eligibility for re-treatment	x			x				
Physical Examination	x[8]			x[8]			x[4-8]	x[5]
Body weight	x			x			x[4]	x
ECOG performance score	x			x			x[4]	x
Pregnancy test	x			x			x[4]	
12-lead-ECG	x[6-14]	x[14]	x[14]	x[6-14]	x[14]	x[14]	x[14]	x[5-14]
LVEF[15]			x[15]				x[16]	x[5]
Dispensing of BI 894999	**x**			**x**				
Intake of BI 894999	**x**[7]	**-------**	**---------**	**x**[7]	**-------**	**x**[7]		
Compliance check			x			x	x	
Vital Signs	x	x	x	x		x	x	
Safety lab parameters	x[18]	x	x	x[18]	x[17]	x[17]	x[18]	x[5]
Tumour markers	x[19]			x[19]				
Urine examination	x			x			x	
Pharmacokinetics		x[9]						
Adverse Events	x	x	x	x	x	x	x	x[10]
Concomitant Therapy	x[11]	x	x	x	x	x	x	x[10]
CT and/or MRI - PET/CT in DLBCL[12]			x[12]			x[12]	x[12]	x[12]
Bone Marrow in DLBCL when CR[12]			x[12]			x[12]		
Bone scan in mCRPC						x[12]		
Tumour assessment[12]			x[12]			x[12]	x[12]	x[12]
Optional archival tumour tissue	x[13]							
Optional fresh tumour biopsy	x[13]							
Mandatory DNA blood[13]	x[13]							
Termination of study medication							x	
Patient's status (alive/PD/dead)								x

*this intermediate visit during a cycle becomes optional starting from C5 onwards if there are no concerns regarding cardiac safety of the patient (normal or stable CK, troponin, ECG, LVEF)

** Schedule A Flow Chart not updated in this version of the protocol except for the body weight cross at follow-up visit, which was missing in error, since no new patients will be included in this schedule at the time of creation of protocol version 9.0

[1] end of treatment; investigations which have to be performed at the EOT visit (as soon as possible when a patient discontinues treatment)

[2] FU= follow up visit until progression, lost to follow up, treatment with another anti-cancer drug or end of the whole trial as specified in Section 8.6. The first follow-up visit is the End of Residual Effect Period visit (EOR) which must happen at the earliest 30 days after the end of treatment (see Section 6.2.3.2)

[3] last visit of a cycle may correspond to visit 1 of next Cycle if an additional cycle is indicated
[4] data from the last visit of the previous cycle (Day 22) may be used in case examinations were done within the past two weeks
[5] optional, to perform if needed to follow-up on AEs present/ongoing at previous visit or if not performed at the EOT visit
[6] ECG must be repeated pre-dose on C2V1 (or CxV1) if C2V1 (or CxV1) happens on a different day than C1V5 (or last visit of previous cycle)
[7] the first dose of the cycle is administered on site, all other doses are taken by the patient outside the clinical site
[8] In DLBCL patients, the physical examination will include a tumour evaluation (largest palpable lymph node per area, measured in two dimensions if one diameter at least is > 1cm, evaluation of spleen and liver enlargement by measuring the cm below costal margin and two dimensional evaluation of any other palpable tumour manifestation)
[9] At any time, only in case of drug related Grade 3 or Grade 4 toxicity, every effort must be made to collect a PK sample; date and time of the sample and of the most recent drug intake (before PK sample) need to be recorded for such samples
[10] all AEs and concomitant medication must be collected until 30 days (until EOR) after the last BI 894999 intake. After EOR, for subsequent FU visits, only SAEs/AESIs which are considered study drug related need to be collected as well as their related treatment
[11] update only
[12] according to RECIST 1.1 guidelines for patients with solid tumours (including mCRPC patients who have a measurable disease). Imaging and assessment are required every 2 cycles (meaning every 6 weeks if no delays in cycles but as close as possible to the end of the second of the two cycles of treatment if there was a delay). EOT/ FU imaging and assessment are optional if previous exam was performed in the past 4 weeks. The choice of computed tomography (CT) and/or magnetic resonance imaging (MRI) is left to the investigator's judgement but the method must remain the same for all evaluations. If the patient did not end the trial treatment due to progressive disease (PD), the tumour assessments during follow-ups will be according to standard of care for the site/country.
For mCRPC patients, in addition to the CT/MRI every 2 cycles, a bone scan has to be performed at screening and then every 4 cycles (every 12 weeks if no delays in cycles) with a PSA evaluation at the same time-points as the bone scan.
According to RECIL 2017 guidelines for DLBCL patients, a FDG-PET coupled to a CT scan (or MRI if CT not possible but each time, same method) must be performed at screening, at the end of Cycle 2 (at 6 weeks if no delays in cycles), at the end of Cycle 4 (week 12) and then every 4 cycles. In case a complete response is observed, a BM aspirate and biopsy have to be performed for confirmation of CR
[13] If a patient has an objective response or is benefiting from the treatment and he/she agreed beforehand for sending of archival tumour tissue or/and for a fresh tumour biopsy (if deemed safe and feasible by the investigator) for gene analysis, 2-3 mL EDTA DNA blood tube at any time during response
[14] For each ECG, digitalized triplicate acquisition using dedicated equipment for central reading by clinical research organization (CRO). The ECGS are to be performed before the blood sampling when at same time-point as blood sampling (see 5.4.2)
[15] to be performed at the end of Cycle 2 by echocardiography or MUGA scan, by the same method as at baseline
[16] to be performed if not done in the past 6 weeks and if possible, according to the patient's condition at the time of EOT
[17] measurements of CK and troponin and any other parameter deemed necessary to be controlled by the investigator
[18] including measurements of coagulation parameters: aPTT, PT expressed in seconds and INR
[19] PSA mandatory for mCRPC patients

FLOW CHART FIRST TREATMENT CYCLE IN SCHEDULE B

Study Periods	**Screen**	**Treatment Cycle 1**									**EOT**[1]	**FU**[2]
Visit	**Screen**	**1**			**2**	**3**	**4**			**5**[3]	**EOT**	**FU**
Day (day range)	**-28 - 1**	**1**	**2**	**3**[4]	**8 (± 1)**	**12 (± 1)**	**14**	**15**	**18 (± 1)**	**22**		**FU1 = EOR +30 (+7) after EOT**
Informed Consents[5]	x											
Demographics	x											
Medical History	x											
In- /Exclusion Criteria	x	x										
Physical Examination	x	x									x	x[6]
Height	x											
Body weight	x	x									x	x
ECOG performance score	x	x									x	x
Pregnancy test	x[7]										x	
12-lead-ECG	x	x[8]	x[8]		x[8]		x[8]	x[8]		x[8]	x[8]	x[6]
LVEF[9]	x										x[22]	x[6]
Dispensing of BI 894999		**x**										
Intake of BI 894999		**x**[10]	**x**[10]	**x**[10]	**x**[10]	**x**[10]	**x**[10]					
Compliance check					x	x	x				x	
Completion of diary card[11]		x---	----	----	----	----	---x					
Vital Signs	x	x[12]	x	x	x	x	x[12]	x	x	x	x	
Safety lab parameters	x[13-13b]	x[13-13a]	x[13]		x[13]		x[13-13a]			x[13]	x[13]	x[6]
Tumour markers[14]	x											
Urine examination[15]	x	x	x				x			x	x	
Pharmacokinetics (plasma)		x[16]	x[16]	x[16]	x[16]	x[16]	x[16]	x[16]	x[16]			
Pharmacokinetics (urine)		x[17]	x[17]				x[17]	x[17]				
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x[18]
Concomitant Therapy	x	x	x	x	x	x	x	x	x	x	x	x[18]
CT and/or MRI-PET/CT in DLBCL[19]	x[19]										x[19]	x[6]
Bone scan in mCRPC	x											
Tumour assessment[19]	x										x[19]	x[6]
Tumour biopsy for exploratory biomarker analysis[20-a-b]	x[20-a]				x[20-a-b]							
Mandatory DNA blood[20-a-b]	x				x							
[redacted] gene expression in whole blood		x[21]	x[21]				x[21]	x[21]	x[21]			
Optional bio-banking sample		x										
Termination of study medication											x	
Overall clinical benefit assessment by Investigator for NC patients											x	
Patient's status (alive/PD/dead)												x[23]

[1] end of treatment (EOT) investigations which have to be performed at the EOT visit (as soon as possible when a patient discontinues treatment)

[2] FU= follow up visits until progression, lost to follow up, treatment with another anti-cancer drug or end of the whole trial as specified in Section 8.6. The first follow-up visit is the End of Residual Effect Period visit (EOR) which must happen at the earliest 30 days after the end of treatment (see Section 6.2.3.2)

[3] visit 5 of Cycle 1 may correspond to visit 1 of Cycle 2 if an additional cycle is indicated

[4] patients recruited for the food interaction cohorts must have one PK sampling on Day 3 (approximately 24h after BI 894999 intake on Day 2). See Appendix 10.2 for further details

[5] the informed consent consist of 2 forms (or different sections, depending on the countries):

- a main informed consent for participation to the trial including a separate sub-section for participation to the food interaction sub-study and
- a separate informed consent for biomarkers analyses:
  - mandatory blood samples for pharmacogenomics,
  - optional bio-banking sample for pharmacogenomics
  - tumour biopsies for pharmacogenomics biomarkers analyses
    - optional in escalation part until MTD in patients with solid tumours and in DLBCL cohort
    - optional in MTD extension part in patients with solid tumours and in DLBCL cohort
    - mandatory in Phase Ib expansion at Screening and in Cycle 1 at steady state in patients with solid tumours For patients with NC, and mCRPC with only bone lesions, the biopsies are not requested (remain optional for NC) as well as for patients with therapeutic INR because of treatment with a vitamin K antagonist or a novel oral anticoagulant. The on treatment biopsy may remain optional if no easily accessible lesions are available. The screening biopsy may be replaced by sending of archival tumour tissue from a biopsy taken from the latest relapse and not older than 6 months.
  - optional consent for sending of archival tissue for genomic analysis in case of objective response or if patient is benefiting from treatment
  - optional consent for a fresh tumour biopsy in patients who have an objective response or are benefiting from treatment
  - mandatory consent for an additional 2-3 mL EDTA Blood DNA tube whenever tumour tissue is sent (from fresh tumour biopsy or archival tumour tissue)

For the NC indication, when patients are aged between 15 and <18 years, they will have to sign an assent form for the main part of the trial as well as for the biomarker part while parents (both or one according to national regulation) or the legal guardian must sign both consent forms.

[6] optional, to perform if needed to follow-up on adverse events (AE) present/ongoing at previous visit or if not performed at the EOT visit

[7] a serum or urine beta human chorionic gonadotrophin (βHCG) pregnancy test must be performed within 7 days prior to first treatment in women of childbearing potential

[8] at screening, on Days 1-2 and 14-15: pre-dose and at approximately 2h, 4h, 8h, 24h post-dose, as well as on Days 8 and 22 of Cycle 1, and at EOT, at any time of the visit when not on an intensive PK day. For each ECG, digitalized triplicate acquisition using dedicated equipment for central reading by clinical research organization (CRO). The ECGS are to be performed before the blood sampling when at same time-point as blood sampling (see 5.4.2)

[9] by echocardiography or MUGA scan, but each time by the same method

[10] intake of BI 894999 done at the clinical site on Days 1, 2, 8, 12, 14, and by the patient anywhere else on the other days (between Day 1 and Day 14). The patient may take the medication before arriving at the clinical site on the day of biopsy at steady state in Cycle 1 if performed on a different day then Day 8 but must clearly note the exact hour of intake

[11] the diary card must be completed every day of intake in Cycle 1

[12] vital signs (blood pressure, pulse and body temperature): on days 1 and 14: pre-dose, and approximately 4h, 8h post-dose. On all other visit days, once at any time during the visit day

[13] When a blood glucose test is performed, the investigator must indicate whether the patient was in fasting condition at the time of the blood sampling, meaning the sample is taken after an overnight fasting. Safety lab parameters including coagulation parameters (aPTT, PT expressed in sec and INR) only to be performed at screening, on Day 1 pre-dose, on Day 2, Day 8, pre-dose on the day of tumour biopsy when applicable (if on a different day then Day 8), on Day 14 and at EOT. Each time a safety lab is foreseen per protocol, troponin hs test must be performed (T hs or I hs but always the same test for a given patient).

[13a] In the first 20 patients to be entered in phase Ib after approval of protocol version 7.0, coagulation factors II, V, VII and IX will be measured on C1D1 pre-dose, on C1D14 pre-dose and on C2V1D1 pre-dose.

[13b] Hep B DNA test, Hep C RNA test and HIV infection detection by an established HIV diagnostic assay performed at screening (results within 4 weeks before screening are acceptable) .

[14] only in patients with tumour types where there is a clinically relevant tumour marker which is already used in routine clinical practice for tumour restaging (on Day 1 of every cycle). PSA mandatory for mCRPC patients

[15] urine examination by dipstick for pH, glucose, erythrocytes, leukocytes, protein, nitrite. If pathological findings, further evaluation (see Section 5.3.3)

[16] intensive PK blood sampling will be performed in Cycle 1, as summarized in Appendix 10.2
For the food interaction cohorts, same PK time points as for other patients with in addition on Day 2: 0:30min, 1h, 2h, 3h, 4h, 6h, 8h 24h (Days 2) post-dose and on Day 3: 24h post-dose of Day 2 (see 10.2.2)
Pre-dose sampling will be conducted at Days 8 and 12 just before drug administration of the dose
A PK sample will also be taken at the time of the visit on Day 18

[17] one blank urine will be collected prior to the BI 894999 intake on visit 1 and visit 4 (at least two 2 mL aliquots). In addition urine will be collected as summarized in Appendix 10.2

[18] all AEs and concomitant medication must be collected until 30 days (until EOR) after the last BI 894999 intake. After EOR, for subsequent FU visits, only SAEs/AESIs which are considered study drug related need to be collected as well as their related treatment

[19] according to RECIST 1.1 guidelines for patients with solid tumours (including mCRPC patients who have a measurable disease). Imaging and assessment are required every 2 cycles (meaning every 6 weeks if no delays in cycles but as close as possible to the end of the second of the two cycles of treatment if there was a delay). EOT/FU imaging and assessment are optional if previous examination was performed in the past 6 weeks
For mCRPC patients, in addition to the CT/MRI every 2 cycles, a bone scan has to be performed at screening and then every 4 cycles (every 12 weeks if no delays in cycles) with a PSA evaluation at the same time-points as the bone scan.
According to RECIL 2017 guidelines for DLBCL patients, a FDG-PET/CT scan (or MRI if CT not possible but each time same method) must be performed at screening, at the end of Cycle 2 (at 6 weeks if no delays in cycles), at the end of Cycle 4 (week 12) and then every 4 cycles. EOT/ FU imaging and assessment are optional if previous exam was performed in the past 6 weeks

[20a] optional for patients in the escalation phase including the patients in the extension of MTD cohort who agree to tumour biopsy and mandatory for patients in the expansion Phase Ib, a tumour biopsy for biomarker analysis (see 5.5.1.2) must be performed at baseline and between Day 8 and Day 11 (4-8hrs after drug intake) of Cycle 1: the biopsy may only be performed if the platelet count is above 50 000/mm^3 without support from a transfusion and coagulation parameters (aPTT, PT in sec and INR) are within normal limits on the day of the biopsy. The baseline biopsy may be replaced by the sending of archival tumour tissue from a biopsy performed at the latest progression and not older than 6 months. For those patients having a tumour biopsy or sending of archival tumour tissue, a mandatory 2-3 mL EDTA DNA blood sample must be taken once, at any time, being it at screening or with steady state biopsy. In Phase Ib, for mCRPC patients with only bone metastases and for NC patients, tumour biopsies are not requested (remain optional) as well as for patients with therapeutic INR because of treatment with a vitamin K antagonist or a novel oral anticoagulant. The on treatment biopsy may remain optional if no easily accessible lesions are available

[20b] if abnormal coagulation parameters and/or a platelet count below 50 000/mm^3 prevent tumour biopsies between Day 8 and Day 11 of Cycle 1 in 5 or more of the 20 first patients of Phase Ib in solid tumours, the window for tumour biopsy will be moved ahead between Day 3 and Day 8 (4-8hrs after drug intake) in the further entered patients. Where a fresh biopsy is taken for the baseline sample the subsequent on-treatment biopsy should be taken, where feasible, from the same lesion (not to be considered as a target lesion)

[redacted] (or other genes related to MOA) gene expression will be analysed in whole blood as summarized in Appendix 10.2

[22] to be done if not performed within the previous 6 weeks and if possible, according to the patient's condition at the time of EOT

[23] for NC patients recruited in Phase Ib after approval of protocol version 11.0, the patient's survival status will continue to be collected until death, lost to follow-up or until 12 months after the end of trial, even if the patient progressed according to RECIST 1.1 or started with another anti-cancer treatment, according to patient's informed consent

FLOW CHART: SECOND AND FURTHER TREATMENT CYCLES IN SCHEDULE B

Study Periods	**Treatment Cycles**							**EOT**[1]	**FU**[2]
Visit	**C2V1**		**C2V2**	**C2V3**[3]	**CxV1**		**CxV2**[3]	**EOT**	**FU**
Day (day range)	**1**	**2**	**15 (-4+2)**	**22**	**1**	**15 (-4+2)***	**22**		**First = EOR +30 (+7) after EOT**
Eligibility for re-treatment	x				x				
Physical Examination	x				x			x[4]	x[5]
Body weight	x				x			x[4]	x
ECOG performance score	x				x			x[4]	x
Pregnancy test	x				x			x[4]	
12-lead-ECG	x[6-18]		x[18]	x[18]	x[6-18]	x[18]	x[18]	x[18]	x[5-18]
LVEF				x[15]				x[16]	x[5]
Dispensing of BI 894999	**x**				**x**				
Intake of BI 894999 from Day 1 till Day 14 of a cycle	**x**[7]	**x**[7]			**x**[7]				
Compliance check				x			x	x	
Vital Signs	x	x	x	x	x		x	x	
Safety lab parameters	x[19-19a]		x[19]	x[19]	x[19]	x[17-19]	x[17-19]	x[19]	x[5]
Tumour markers	x[20]				x[20]				
Urine examination	x				x			x	
Pharmacokinetics	x[8]	x[8]	x[9]						
Adverse Events	x	x	x	x	x	x	x	x	x[10]
Concomitant Therapy	x[11]	x	x	x	x	x	x	x	x[10]
CT and/or MRI – PET/CT in DLBCL[12]				x[12]			x[12]	x[12]	x[12]
Bone scan in mCRPC							x[12]		
Tumour assessment[12]				x[12]			x[12]	x[12]	x[12]
[redacted]1 gene expression in whole blood[13]	x[13]	x[13]							
Optional archival tumour tissue:	x[14]								
Optional fresh tumour biopsy	x[14]								
Mandatory DNA blood[14]	x[14]								
Termination of study medication								x	
Overall clinical benefit assessment by Investigator for NC patients								x	
Patient's status (alive/PD/dead)									x[21]

*this intermediate visit during a cycle becomes optional starting from C5 onwards if there are no concerns regarding cardiac safety of the patient (normal or stable CPK, troponin, ECG, LVEF)

[1] end of treatment; investigations which have to be performed at the EOT visit (as soon as possible when a patient discontinues treatment)
[2] FU= follow up visit until progression, lost to follow up, treatment with another anti-cancer drug or end of the whole trial as specified in Section 8.6. The first follow-up visit is the End of Residual Effect Period visit (EOR) which must happen at the earliest 30 days after the end of treatment (see Section 6.2.3.2)
[3] last visit of a cycle may correspond to visit 1 of next Cycle if an additional cycle is indicated
[4] data from the last visit of the previous cycle (Day 22) may be used in case examinations were done within the past two weeks
[5] optional, to perform if needed to follow-up on AEs present/ongoing at previous visit or if not performed at the EOT visit
[6] ECG must be repeated pre-dose on C2V1 (or CxV1) if C2V1 (or CxV1) happens on a different day than C1V5 (or last visit of previous cycle)
[7] the first (and second for C2) doses of the cycle are administered on site, all other doses are taken by the patient outside the clinical site
[8] PK blood sampling before intake of BI 894999, only in Cycle 2 Days 1-2 (see Appendix 10.2)
[9] At any time, only in case of drug related Grade 3 or Grade 4 toxicity, every effort must be made to collect a PK sample; date and time of the sample and of the most recent drug intake (before PK sample) need to be recorded for such samples
[10] all AEs and concomitant medication must be collected until 30 days (until EOR) after the last BI 894999 intake. After EOR, for subsequent FU visits, only SAEs/AESIs which are considered study drug related need to be collected as well as their related treatment
[11] update only
[12] according to RECIST 1.1 guidelines for patients with solid tumours (including mCRPC patients who have a measurable disease). Imaging and assessment are required every 2 cycles (meaning every 6 weeks if no delays in cycles but as close as possible to the end of the second of the two cycles of treatment if there was a delay). EOT/ FU imaging and assessment are optional if previous exam was performed in the past 6 weeks. The choice of computed tomography (CT) and/or magnetic resonance imaging (MRI) is left to the investigator's judgement but the method must remain the same for all evaluations. If the patient did not end the trial treatment due to progressive disease (PD), the tumour assessments during follow-ups will be according to standard of care for the site/country.
For mCRPC patients, in addition to the CT/MRI every 2 cycles, a bone scan has to be performed at screening and then every 4 cycles (every 12 weeks if no delays in cycles) with a PSA evaluation at the same time-points as the bone scan.
According to RECIL 2017 guidelines for DLBCL patients, a FDG-PET/CT scan (or MRI if CT not possible but each time same method) must be performed at screening, at the end of Cycle 2 (at 6 weeks if no delays in cycles), at the end of Cycle 4 (week 12) and then every 4 cycles with interpretation according to RECIL 2017 guidelines. EOT/ FU imaging and assessment are optional if previous exam was performed in the past 6 weeks
[13] Gene expression will be analysed in whole blood which must be collected as summarized in Appendix 10.2
[14] If a patient has an objective response or is benefiting from the treatment and he/she agreed beforehand for sending of archival tumour tissue or/and for a fresh tumour biopsy (if deemed safe and feasible by the investigator) for gene analysis, 2-3 mL EDTA DNA blood tube at any time (if not yet done before)
[15] to be performed by echocardiography or MUGA scan, by the same method as at baseline
[16] to be performed if not done in the past 6 weeks and if possible, according to the patient's condition at the time of EOT
[17] measurements of CK and troponin and any other parameter deemed necessary to be controlled by the investigator
[18] For each ECG, digitalized triplicate acquisition using dedicated equipment for central reading by clinical research organization (CRO). The ECGS are to be performed before the blood sampling when at same time-point as blood sampling (see 5.4.2)
[19] When a blood glucose test is performed, the investigator must indicate whether the patient was in fasting condition at the time of the blood sampling, meaning the sample is taken after an overnight fasting. Safety lab parameters including measurements of coagulation parameters: aPTT, PT expressed in seconds and INR. Each time a safety lab is foreseen per protocol, troponin hs test must be performed (T hs or I hs but always the same test for a given patient).Coagulation parameters will be evaluated on V1 and V2 of Cycles 2, 3 and 4 and on V1 from Cycle 5 onwards.

[19a] In the first 20 patients to be entered in phase Ib after approval of protocol version 7.0, coagulation factors II, V, VII and IX will be measured on C1D1 pre-dose, on C1D14 pre-dose and on C2V1D1 pre-dose.
[20] PSA mandatory for mCRPC patients
[21] for NC patients recruited in Phase Ib after approval of protocol version 11.0, the patient's survival status will continue to be collected until death, lost to follow-up or until 12 months after the end of trial, even if the patient progressed according to RECIST 1.1 or started with another anti-cancer treatment, according to patient's informed consent

FLOW CHART FIRST TREATMENT CYCLE IN SCHEDULE C FOR SOLID TUMOUR PATIENTS IN PHASE IA

Study Periods	**Screen**	**Treatment Cycle 1**							**EOT**[1]	**FU**[2]
Visit	**Screen**	**1**		**2**	**3**	**4**		**5**[3]	**EOT**	**FU**
Day (day range)	**-28 - 1**	**1**	**2**	**8**	**15**	**21**	**22**	**29**		**FU1 = EOR +30 (+7) after EOT**
Informed Consents[4]	x									
Demographics	x									
Medical History	x									
In- /Exclusion Criteria	x	x								
Physical Examination	x	x							x	x[5]
Height	x									
Body weight	x	x							x	x
ECOG performance score	x	x							x	x
Pregnancy test	x[6]								x	
12-lead-ECG	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]	x[5]
LVEF[8]	x								x[20]	x[5]
Dispensing of BI 894999		**x**								
Intake of BI 894999		**x**[9]	**x**[9]		**x**[9]	**x**[9]				
Compliance check				x		x			x	
Completion of diary card[10]		x---	---x		x----	----x				
Vital Signs	x	x[11]	x	x	x	x[11]	x	x	x	
Safety lab parameters	x[12-12a]	x[12]	x[12]	x[12]	x[12]	x[12]		x[12]	x[12]	x[5]
Tumour markers[13]	x									
Urine examination[14]	x	x	x					x	x	
Pharmacokinetics (plasma)		x[15]	x[15]	x[15]		x[15]	x[15]	x[15]		
Adverse Events	x	x	x	x	x	x	x	x	x	x[16]
Concomitant Therapy	x	x	x	x	x	x	x	x	x	x[16]
CT and/or MRI - [17]	x[17]								x[17]	x[5]
Tumour assessment[17]	x								x[17]	x[5]
Tumour biopsy for exploratory biomarker analysis[18-a-b]	x[189-a]					x[18-a-b]				
Mandatory DNA blood[18-a-b]	x[18-a-b]					x[18-a-b]				
[redacted] gene expression in whole blood[19]		x[19]	x[19]			x[19]	x[19]			
Optional bio-banking sample		x								
Termination of study medication									x	
Patient's status (alive/PD/dead)										x

[1] end of treatment (EOT) investigations which have to be performed at the EOT visit (as soon as possible when a patient discontinues treatment)

[2] FU= follow up visits until progression, lost to follow up, treatment with another anti-cancer drug or end of the whole trial as specified in Section 8.6. The first follow-up visit is the End of Residual Effect Period visit (EOR) which must happen at the earliest 30 days after the end of treatment (see Section 6.2.3.2)

[3] Visit 5 of Cycle 1 may correspond to Visit 1 of Cycle 2 if an additional cycle is indicated

[4] the informed consent consist of 2 forms (or different sections, depending on the countries):

- a main informed consent for participation to the trial
- a separate informed consent for biomarkers analyses:
  - mandatory blood samples for pharmacogenomics,
  - optional bio-banking sample for pharmacogenomics
  - optional tumour biopsies for pharmacogenomics biomarkers analyses
  - optional consent for sending of archival tissue for genomic analysis in case of objective response or if patient is benefiting from treatment
  - optional consent for a fresh tumour biopsy in patients who have an objective response or are benefiting from treatment
  - mandatory consent for an additional 2-3 mL EDTA Blood DNA tube, if consent is given for archival/fresh tumour biopsy

[5] optional, to perform if needed to follow-up on adverse events (AE) present/ongoing at previous visit or if not performed at the EOT visit

[6] a serum or urine beta human chorionic gonadotrophin (βHCG) pregnancy test must be performed within 7 days prior to first treatment in women of childbearing potential

[7] at Screening, on Days 1-2 and 21-22: pre-dose and at approximately 2h, 4h, 8h, 24h post-dose, on Days 8 and 15, as well as on Day 29 of Cycle 1, and at EOT, at any time of the visit when not on an intensive PK day. For each ECG, digitalized triplicate acquisition, using dedicated equipment for central reading by clinical research organization (CRO). The ECGS are to be performed before the blood sampling when at same time-point as blood sampling (see Section 5.4.2)

[8] by echocardiography or MUGA scan, but each time by the same method

[9] intake of BI 894999 done at the clinical site on Days 1, 2, 15 and on Day 21, and by the patient anywhere else on the other days (between Day 3 and Day 7 and between Day 16 and Day 20). On the day of biopsy, if not performed on Day 21, the patient may take the medication before arriving at the clinical site but must note the exact hour of intake

[10] the diary card must be completed every day of intake in Cycle 1

[11] vital signs (blood pressure, pulse and body temperature): on Days 1 and 21: pre-dose, and approximately 4h, 8h post-dose. On all other visit days, once at any time during the visit day

[12] When a blood glucose test is performed, the investigator must indicate whether the patient was in fasting condition at the time of the blood sampling, meaning the sample is taken after an overnight fasting. Safety lab parameters including coagulation parameters (aPTT, PT expressed in sec and INR) only to be performed at screening, on Day 1 pre-dose, on Day 2, Day 8, Day 21, pre-dose and on the day of tumour biopsy when applicable (if on a different day then Day 21), and at EOT. Each time a safety lab is foreseen per protocol, troponin hs test must be performed (T hs or I hs but always the same test for a given patient).

[12a] Hep B DNA test, Hep C RNA test and HIV infection detection by an established HIV diagnostic assay performed at screening (results within 4 weeks before screening are acceptable)

[13] only in patients with tumour types where there is a clinically relevant tumour marker which is already used in routine clinical practice for tumour restaging (on Day 1 of every cycle)

[14] urine examination by dipstick for pH, glucose, erythrocytes, leukocytes, protein, nitrite. If pathological findings, further evaluation (see Section 5.3.3)

[15] intensive PK blood sampling will be performed in Cycle 1, as summarized in Appendix 10.2.
A PK sample will also be taken at the time of the visit on Day 8 and on Day 29

[16] all AEs and concomitant medication must be collected until 30 days (until EOR) after the last BI 894999 intake. After EOR, for subsequent FU visits, only SAEs/AESIs which are considered study drug related need to be collected as well as their related treatment

[17] according to RECIST 1.1 guidelines for patients with solid tumours. Imaging and assessment are required every 2 cycles (meaning every 8 weeks if no delays in cycles but as close as possible to the end of the second of the two cycles of treatment if there was a delay). EOT/FU imaging and assessment are optional if previous examination was performed in the past 6 weeks

[18a]optional for patients in the escalation phase including the patients in the extension of MTD cohort, who agree to tumour biopsy, a tumour biopsy for biomarker analysis (see Section 5.5.1.2) may be performed at baseline and between Day 18 and Day 21 (4-8h after drug intake) of Cycle 1: the biopsy may only be performed if the platelet count is above 50 000/mm^3 without support from a transfusion and coagulation parameters (aPTT, PT in sec and INR) are within normal limits on the day of the biopsy. For those patients having a tumour biopsy or sending of archival tumour tissue, a mandatory 2-3 mL EDTA DNA blood sample must be taken once, being it at screening or when steady state tumour biopsy is taken.

[18b]Where a fresh biopsy is taken for the baseline sample the subsequent on-treatment biopsy should be taken, where feasible, from the same lesion (not to be considered as a target lesion)

[redacted] (or other genes related to MOA) gene expression will be analysed in whole blood as summarized in Appendix 10.2

[20] to be done if not performed within the previous 6 weeks and if possible, according to the patient's condition at the time of EOT

FLOW CHART: SECOND AND FURTHER TREATMENT CYCLES IN SCHEDULE C FOR SOLID TUMOUR PATIENTS IN PHASE IA

Study Periods	**Treatment Cycles**						**EOT**[1]	**FU**[2]
Visit	**C2V1**	**C2V2**	**C2V3**[3]	**CxV1**		**CxV2**[3]	**EOT**	**FU**
Day (day range)	**1**	**15**	**29**	**1**	**15**	**29**		**First = EOR +30 (+7) after EOT**
Eligibility for re-treatment	x			x				
Physical Examination	x			x			x[4]	x[5]
Body weight	x			x			x[4]	x
ECOG performance score	x			x			x[4]	x
Pregnancy test	x			x			x[4]	
12-lead-ECG	x[6-16]	x[16]	x[16]	x[6-16]	x[16]	x[16]	x[16]	x[5-16]
LVEF			x[13]				x[14]	x[5]
Dispensing of BI 894999	**x**			**x**				
Intake of BI 894999	**x**[7]	**x**[7]		**x**[7]	**x**[7]			
Compliance check			x			x	x	
Vital Signs	x	x	x	x	x	x	x	
Safety lab parameters	x[17]	x[17]	x[17]	x[17]	x[15-17]	x[15-17]	x[17]	x[5]
Tumour markers	x			x				
Urine examination	x			x			x	
Pharmacokinetics				x[8]				
Adverse Events	x	x	x	x	x	x	x	x[9]
Concomitant Therapy	x[10]	x	x	x	x	x	x	x[9]
CT and/or MRI[11]			x[11]			x[11]	x[11]	x[11]
Tumour assessment[11]			x[11]			x[11]	x[11]	x[11]
Optional archival tumour tissue:				x[12]				
Optional fresh tumour biopsy				x[12]				
Mandatory DNA blood[12]				x[12]				
Termination of study medication							x	
Patient's status (alive/PD/dead)								x

[1] end of treatment; investigations which have to be performed at the EOT visit (as soon as possible when a patient discontinues treatment)

[2] FU= follow up visit until progression, lost to follow up, treatment with another anti-cancer drug or end of the whole trial as specified in Section 8.6. The first follow-up visit is the End of Residual Effect Period visit (EOR) which must happen at the earliest 30 days after the end of treatment (see Section 6.2.3.2)

[3] last visit of a cycle may correspond to visit 1 of next Cycle if an additional cycle is indicated

[4] data from the last visit of the previous cycle (Day 29) may be used in case examinations were done within the past two weeks

[5] optional, to perform if needed to follow-up on AEs present/ongoing at previous visit or if not performed at the EOT visit

[6] ECG must be repeated pre-dose on C2V1 (or CxV1) if C2V1 (or CxV1) happens on a different day than C1V5 (or last visit of previous cycle)

[7] from Day 1 till Day 7 and from Day 15 till Day 21 of a cycle with a loading dose on Days 1 and 15. The doses of Day 1 and Day 15 of the cycle are administered on site, all other doses are taken by the patient outside the clinical site

[8] at any time, only in case of drug related Grade 3 or Grade 4 toxicity, every effort must be made to collect a PK sample; date and time of the sample and of the most recent drug intake (before PK sample) need to be recorded for such samples

[9] all AEs and concomitant medication must be collected until 30 days (until EOR) after the last BI 894999 intake. After EOR, for subsequent FU visits, only SAEs/AESIs which are considered study drug related need to be collected as well as their related treatment

[10] update only

[11] according to RECIST 1.1 guidelines for patients with solid. Imaging and assessment are required every 2 cycles (meaning every 8 weeks if no delays in cycles but as close as possible to the end of the second of the two cycles of treatment if there was a delay). EOT/ FU imaging and assessment are optional if previous exam was performed in the past 6 weeks. The choice of computed tomography (CT) and/or magnetic resonance imaging (MRI) is left to the investigator's judgement but the method must remain the same for all evaluations. If the patient did not end the trial treatment due to progressive disease (PD), the tumour assessments during follow-ups will be according to standard of care for the site/country

[12] If a patient has an objective response or is benefiting from the treatment and he/she agreed beforehand for sending of archival tumour tissue or/and for a fresh tumour biopsy (if deemed safe and feasible by the investigator) for gene analysis, 2-3 mL EDTA DNA blood tube at any time, if not yet done before

[13] to be performed by echocardiography or MUGA scan, by the same method as at baseline

[14] to be performed if not done in the past 6 weeks and if possible, according to the patient's condition at the time of EOT

[15] measurements of CK and troponin and any other parameter deemed necessary to be controlled by the investigator

[16] For each ECG, digitalized triplicate acquisition using dedicated equipment for central reading by clinical research organization (CRO). The ECGS are to be performed before the blood sampling when at same time-point as blood sampling (see Section 5.4.2)

[17] When a blood glucose test is performed, the investigator must indicate whether the patient was in fasting condition at the time of the blood sampling, meaning the sample is taken after an overnight fasting. Safety lab parameters including measurements of coagulation parameters: aPTT, PT expressed in seconds and INR. Each time a safety lab is foreseen per protocol, troponin hs test must be performed (T hs or I hs but always the same test for a given patient).
Coagulation parameters will be evaluated only on V1 of each cycle.

FLOW CHART FIRST TREATMENT CYCLE IN SCHEDULE C FOR DLBCL PATIENTS IN PHASE IA AND NC PATIENTS IN PHASE IB

Study Periods	**Screen**	**Treatment Cycle 1**						**EOT**[1]	**FU**[2]
Visit	**Screen**	**1**	**2***	**3**	**4**		**5**[3]	**EOT**	**FU**
Day (day range)	**-28 - 1**	**1**	**8**	**15**	**21**	**22**	**29**		**FU1 = EOR +30 (+7) after EOT**
Informed Consents[4]	x								
Demographics	x								
Medical History	x								
In- /Exclusion Criteria	x	x							
Physical Examination	x	x						x	x[5]
Height	x								
Body weight	x	x						x	x
ECOG performance score	x	x						x	x
Pregnancy test	x[6]							x	
12-lead-ECG	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]	x[5]
LVEF[8]	x							x[20]	x[5]
Dispensing of BI 894999		**x**							
Intake of BI 894999		**x**[9]		**x**[9]	**x**[9]				
Compliance check			x		x			x	
Completion of diary card[10]		x---		x----	----x				
Vital Signs	x	x[11]	x	x	x[11]	x	x	x	
Safety lab parameters	x[12]-12a	x[12]	x[12]	x[12]	x[12]		x[12]	x[12]	x[5]
Urine examination[13]	x	x					x	x	
Pharmacokinetics (plasma)		x[14]			x[14]	x[14]	x[14]		
Adverse Events	x	x	x	x	x	x	x	x	x[15]
Concomitant Therapy	x	x	x	x	x	x	x	x	x[15]
CT and/or MRI - PET/CT in DLBCL[16]	x[16]							x[16]	x[5]
Tumour assessment[16]	x							x[16]	x[5]
Tumour biopsy for exploratory biomarker analysis[17-a-b]	x[17-a]				x[17-a-b]				
Mandatory DNA blood[17-a-b]	x[17-a-b]				x[17-a-b]				
[redacted]1 gene expression in whole blood[18]		x[18]			x[18]	x[18]			
Optional bio-banking sample		x							
Termination of study medication								x	
Overall clinical benefit assessment by Investigator for NC patients								x	
Patient's status (alive/PD/dead)									x[19]

* Examinations of visit on Day 8 may be performed locally, close to the patient's home, with all tests done as foreseen per protocol and a phone call visit with the Investigator happens to evaluate the patient's safety, if the patient is unable to travel frequently to the site and if allowed by local country regulations

[1] end of treatment (EOT) investigations which have to be performed at the EOT visit (as soon as possible when a patient discontinues treatment)

[2] FU= follow up visits until progression, lost to follow up, treatment with another anti-cancer drug or end of the whole trial as specified in Section 8.6. The first follow-up visit is the End of Residual Effect Period visit (EOR) which must happen at the earliest 30 days after the end of treatment (see Section 6.2.3.2)

[3] Visit 5 of Cycle 1 may correspond to Visit 1 of Cycle 2 if an additional cycle is indicated

[4] the informed consent consist of 2 forms (or different sections, depending on the countries):

- a main informed consent for participation to the trial
- a separate informed consent for biomarkers analyses:
    - mandatory blood samples for pharmacogenomics,
    - optional bio-banking sample for pharmacogenomics
    - optional tumour biopsies for pharmacogenomics biomarkers analyses
    - optional consent for sending of archival tissue for genomic analysis in case of objective response or if patient is benefiting from treatment
    - optional consent for a fresh tumour biopsy in patients who have an objective response or are benefiting from treatment
    - mandatory consent for an additional 2-3 mL EDTA Blood DNA tube, if consent is given for archival/fresh tumour biopsy

For the NC indication, when patients are aged between 15 years and legal adult age, they will have to sign an assent form for the main part of the trial as well as for the biomarker part while parents (both or one according to national regulation) or the legal guardian must sign both consent forms.

[5] optional, to perform if needed to follow-up on adverse events (AE) present/ongoing at previous visit or if not performed at the EOT visit

[6] a serum or urine beta human chorionic gonadotrophin (βHCG) pregnancy test must be performed within 7 days prior to first treatment in women of childbearing potential

[7] at Screening, on Day 1 pre-dose and at approximately 2h and 4h post-dose and on Days 21-22: pre-dose and at approximately 2h, 4h, 8h, 24h post-dose, on Days 8 and 15, as well as on Day 29 of Cycle 1, and at EOT, at any time of the visit when not on an intensive PK day. For each ECG, as far as possible, digitalized triplicate acquisition, using dedicated equipment for central reading by clinical research organization (CRO). The ECGS are to be performed before the blood sampling when at same time-point as blood sampling (see Section 5.4.2). If on Day 8, the patient has the assessments performed locally, the ECG will not be performed on the central reading ECG device and the ECG tracing must be sent to the site which will send it to the Central Reading laboratory for evaluation.

[8] by echocardiography or MUGA scan, but each time by the same method

[9] intake of BI 894999 done at the clinical site on Days 1, 15 and on Day 21, and by the patient anywhere else on the other days (between Day 3 and Day 7 and between Day 16 and Day 20). On the day of biopsy (optional) if not performed on Day 21, the patient may take the medication before arriving at the clinical site but must note the exact hour of intake

[10] the diary card must be completed every day of intake in Cycle 1

[11] vital signs (blood pressure, pulse and body temperature): on Days 1 and 21: pre-dose, and approximately 4h, 8h post-dose. On all other visit days, once at any time during the visit day

[12] When a blood glucose test is performed, the investigator must indicate whether the patient was in fasting condition at the time of the blood sampling, meaning the sample is taken after an overnight fasting. Safety lab parameters including coagulation parameters (aPTT, PT expressed in sec and INR) only to be performed at screening, on Day 1 pre-dose, on Day 8, Day 21, pre-dose and on the day of tumour biopsy when applicable (if on a different day then Day 21), and at EOT. Each time a safety lab is foreseen per protocol, troponin hs test must be performed (T hs or I hs but always the same test for a given patient).

[12a] Hep B DNA test, Hep C RNA test and HIV infection detection by an established HIV diagnostic assay performed at screening (results within 4 weeks before screening are acceptable)

[13] urine examination by dipstick for pH, glucose, erythrocytes, leukocytes, protein, nitrite. If pathological findings, further evaluation (see Section 5.3.3)

[14] intensive PK blood sampling will be performed in Cycle 1, as summarized in Appendix 10.2.

[15] all AEs and concomitant medication must be collected until 30 days (until EOR) after the last BI 894999 intake. After EOR, for subsequent FU visits, only SAEs/AESIs which are considered study drug related need to be collected as well as their related treatment

[16] according to RECIST 1.1 guidelines for patients with solid tumours. Imaging and assessment are required every 2 cycles (meaning every 8 weeks if no delays in cycles but as close as possible to the end of the second of the two cycles of treatment if there was a delay). EOT/FU imaging and assessment are optional if previous examination was performed in the past 6 weeks

According to RECIL 2017 guidelines for DLBCL patients, a FDG-PET/CT scan (or MRI if CT not possible but each time same method) must be performed at screening, at the end of Cycle 2 (at 8 weeks if no delays in cycles), at the end of Cycle 4 (week 16) and then every 4 cycles. EOT/ FU imaging and assessment are optional if previous exam was performed in the past 6 weeks

[17a] optional for DLBCL patients in the escalation phase including the patients in the extension of MTD cohort and optional for NC patients in Phase Ib, who agree to tumour biopsy, a tumour biopsy for biomarker analysis (see Section 5.5.1.2) may be performed at baseline and between Day 18 and Day 21 (4-8h after drug intake) of Cycle 1: the biopsy may only be performed if the platelet count is above 50 000/mm^3 without support from a transfusion and coagulation parameters (aPTT, PT in sec and INR) are within normal limits on the day of the biopsy. For those patients having a tumour biopsy or sending of archival tumour tissue, a mandatory 2-3 mL EDTA DNA blood sample must be taken once, being it at screening or when steady state tumour biopsy is taken.

[17b] Where a fresh biopsy is taken for the baseline sample the subsequent on-treatment biopsy should be taken, where feasible, from the same lesion (not to be considered as a target lesion)

[redacted] (or other genes related to MOA) gene expression will be analysed in whole blood as summarized in Appendix 10.2

[19] only for NC patients recruited in Phase Ib after approval of protocol version 11.0, the patient's survival status will continue to be collected until death, lost to follow-up or until 12 months after the end of trial, even if the patient progressed according to RECIST 1.1 or started with another anti-cancer treatment, according to patient's informed consent

[20] to be done if not performed within the previous 6 weeks and if possible, according to the patient's condition at the time of EOT

FLOW CHART: SECOND AND FURTHER TREATMENT CYCLES IN SCHEDULE C FOR DLBCL PATIENTS IN PHASE IA AND NC PATIENTS IN PHASE IB

Study Periods	**Treatment Cycles**						**EOT**[1]	**FU**[2]
Visit	**C2V1**	**C2V2***	**C2V3**[3]	**CxV1**		**CxV2**[3]	**EOT**	**FU**
Day (day range)	**1**	**15**	**29**	**1****	**15***	**29**		**First = EOR +30 (+7) after EOT**
Eligibility for re-treatment	x			x				
Physical Examination	x			x			x[4]	x[5]
Body weight	x			x			x[4]	x
ECOG performance score	x			x			x[4]	x
Pregnancy test	x			x			x[4]	
12-lead-ECG	x[6-16]	x[16]	x[16]	x[6-16]	x[16]	x[16]	x[16]	x[5-16]
LVEF			x[13]				x[14]	x[5]
Dispensing of BI 894999	**x**			**x**				
Intake of BI 894999	**x**[7]	**x**[7]		**x**[7]	**x**[7]			
Compliance check			x			x	x	
Vital Signs	x	x	x	x	x	x	x	
Safety lab parameters	x[17]	x[17]	x[17]	x[17]	x[15-17]	x[15-17]	x[17]	x[5]
Tumour markers	x			x				
Urine examination	x			x			x	
Pharmacokinetics		x[8]						
Adverse Events	x	x	x	x	x	x	x	x[9]
Concomitant Therapy	x[10]	x	x	x	x	x	x	x[9]
CT and/or MRI - PET/CT in DLBCL[11]			x[11]			x[11]	x[11]	x[11]
Tumour assessment[11]			x[11]			x[11]	x[11]	x[11]
Optional archival tumour tissue:	x[12]							
Optional fresh tumour biopsy	x[12]							
Mandatory DNA blood[12]	x[12]							
Termination of study medication							x	
Overall clinical benefit assessment by Investigator for NC patients							x	
Patient's status (alive/PD/dead)								x[18]

* Examinations of visit on Day 15 may be performed locally, close to the patient's home, with all tests done as foreseen per protocol and a phone call visit with the Investigator happens to evaluate the patient's safety, if the patient is unable to travel frequently to the site and if allowed per local country regulations

** The Day 1 visit of even cycles, from Cycle 6 onwards may also be performed locally, close to the patient's home with all tests done as foreseen per protocol and a phone call visit with the Investigator happens to evaluate the patient's safety, if the patient is unable to travel frequently to the site. It means that a drug dispensation may happen for two consecutive cycles on Day 1 of uneven cycles starting from C5 onwards, after discussion with the Sponsor and if deemed safe by the Investigator

[1] end of treatment; investigations which have to be performed at the EOT visit (as soon as possible when a patient discontinues treatment)

[2] FU= follow up visit until progression, lost to follow up, treatment with another anti-cancer drug or end of the whole trial as specified in Section 8.6. The first follow-up visit is the End of Residual Effect Period visit (EOR) which must happen at the earliest 30 days after the end of treatment (see Section 6.2.3.2)

[3] last visit of a cycle may correspond to visit 1 of next Cycle if an additional cycle is indicated

[4] data from the last visit of the previous cycle (Day 29) may be used in case examinations were done within the past two weeks

[5] optional, to perform if needed to follow-up on AEs present/ongoing at previous visit or if not performed at the EOT visit

[6] ECG must be repeated pre-dose on C2V1 (or CxV1) if C2V1 (or CxV1) happens on a different day than C1V5 (or last visit of previous cycle)

[7] from Day 1 till Day 7 and from Day 15 till Day 21 of a cycle with a loading dose on Days 1 and 15. The doses of Day 1 and Day 15 of the cycle are administered on site if applicable (when the patient has an on site visit), all other doses are taken by the patient outside the clinical site

[8] at any time, only in case of drug related Grade 3 or Grade 4 toxicity, every effort must be made to collect a PK sample; date and time of the sample and of the most recent drug intake (before PK sample) need to be recorded for such samples

[9] all AEs and concomitant medication must be collected until 30 days (until EOR) after the last BI 894999 intake. After EOR, for subsequent FU visits, only SAEs/AESIs which are considered study drug related need to be collected as well as their related treatment

[10] update only

[11] according to RECIST 1.1 guidelines for patients with solid. Imaging and assessment are required every 2 cycles (meaning every 8 weeks if no delays in cycles but as close as possible to the end of the second of the two cycles of treatment if there was a delay). EOT/ FU imaging and assessment are optional if previous exam was performed in the past 6 weeks. The choice of computed tomography (CT) and/or magnetic resonance imaging (MRI) is left to the investigator's judgement but the method must remain the same for all evaluations. If the patient did not end the trial treatment due to progressive disease (PD), the tumour assessments during follow-ups will be according to standard of care for the site/country
According to RECIL 2017 guidelines for DLBCL patients, a FDG-PET/CT scan (or MRI if CT not possible but each time same method) must be performed at screening, at the end of Cycle 2 (at 8 weeks if no delays in cycles), at the end of Cycle 4 (week 16) and then every 4 cycles. EOT/ FU imaging and assessment are optional if previous exam was performed in the past 6 weeks

[12] If a patient has an objective response or is benefiting from the treatment and he/she agreed beforehand for sending of archival tumour tissue or/and for a fresh tumour biopsy (if deemed safe and feasible by the investigator) for gene analysis, 2-3 mL EDTA DNA blood tube at any time, if not yet done before

[13] to be performed by echocardiography or MUGA scan, by the same method as at baseline

[14] to be performed if not done in the past 6 weeks and if possible, according to the patient's condition at the time of EOT

[15] measurements of CK and troponin and any other parameter deemed necessary to be controlled by the investigator

[16] For each ECG, as far as possible, digitalized triplicate acquisition using dedicated equipment for central reading by clinical research organization (CRO). The ECGS are to be performed before the blood sampling when at same time-point as blood sampling (see Section 5.4.2). When the assessments are performed locally, the ECG will not be performed on the central reading ECG device and the ECG tracing must be sent to the site which will send it to the Central Reading laboratory for evaluation.

[17] When a blood glucose test is performed, the investigator must indicate whether the patient was in fasting condition at the time of the blood sampling, meaning the sample is taken after an overnight fasting. Safety lab parameters including measurements of coagulation parameters: aPTT, PT expressed in seconds and INR. Each time a safety lab is foreseen per protocol, troponin hs test must be performed (T hs or I hs but always the same test for a given patient).
Coagulation parameters will be evaluated only on V1 of each cycle.

[18] only for NC patients recruited in Phase Ib after approval of protocol version 11.0 or 12.0 (depending on the country), the patient's survival status will continue to be collected until death, lost to follow-up or until 12 months after the end of trial, even if the patient progressed according to RECIST 1.1 or started with another anti-cancer treatment, according to patient's informed consent

TABLE OF CONTENTS

ABBREVIATIONS

ABC	Activated B-cell
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine amino Transferase
AML	Acute Myeloid Leukaemia
ANOVA	Analysis of variance
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate amino Transferase
AUC	Area under the Curve
BET	Bromodomain and Extraterminal domain
βHCG	Beta Human Chorionic Gonadotrophin
BHM	Bayesian Hierarchical Model
BI	Boehringer Ingelheim
BLQ	Below the Limit of Quantification
BLRM	Bayesian Logistic Regression Model
BP	Blood pressure
CA	Competent Authority
CK	Creatine phosphokinase
CML	Local Clinical Monitor
COO	Cell of Origin
CPT	Cell Preparation Tube
CR	Complete Response
CRA	Clinical Research Associate
CRC	Colorectal Cancer
CRF	Case Report Form
CRO	Clinical Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP	Cytochrome P450 enzymes
DEDP	Drug Exposure During Pregnancy
DEL	Double Expressor Lymphoma
DHL	Double Hit Lymphoma
DILI	Drug Induced Liver Injury
DLBCL	Diffuse Large B-cell Lymphoma
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EOR	End Of Residual effect period

EOT	End Of Treatment
EWOC	Escalation With Overdose Control
FDG	Fluorodeoxyglucose
FMO	Flavin-containing monooxygenases
FU	Follow-Up
GCB	Germinal Centre B-cell
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
Hep B	Hepatitis B
Hep C	Hepatitis C
[redacted]	hexamethylene bis-acetamide inducible 1 [Homo sapiens (human)]
HIV	Human Immunodeficiency Virus
hs	Highly sensitive
IB	Investigator's Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
INR	International Normalized Ratio
i.p.	Intra-peritoneally
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
Kd	Dissociation Constant
LC-MSMS	Liquid Chromatography coupled to tandem Mass Spectrometry
LDH	Lactic Dehydrogenase
LHRH	Luteinizing Hormone-Releasing Hormone
LPLVPE	Last Patient Last Visit Primary Endpoint
LVEF	Left Ventricular Ejection Fraction
MAP	Meta-analytic Predictive
MASCC	Multinational Association of Supportive Care in Cancer
mCRPC	Metastatic Castration Resistant Prostate Cancer
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Drug Regulatory Activities
MM	Multiple Myeloma
MOA	Mechanism of Action
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition scan
MYC	Myelocytomatosis oncogene
NC	NUT Carcinoma
NCI	National Cancer Institute from the USA
NHL	Non-Hodgkin Lymphoma
NOA	Not Analysed
NOAEL	No Observed Adverse Effect Level
NOP	No Peak detectable

NOR	No valid Result
NOS	No Sample
OR	Objective Response
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PDX	Patient Derived Xenograft
PET	Positron Emission Tomography
PFS	Progression Free Survival
PGx	Pharmacogenomics
PI	Principal Investigator
PK	Pharmacokinetics
PR	Partial Response
PSA	Prostate Specific Antigen
PT	Prothrombin Time
RAS	Rat Sarcoma Virus
RBC	Red Blood Cell count
RDC	Remote Data Capture
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
SAE	Serious Adverse Event
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SOP	Standard Operating Procedure
STD	Severely Toxic Dose
TBA	Trial Bio-analyst
TCM	Trial Clinical Monitor
TCPK	Trial Pharmacokineticist
TGI	Tumour Growth Inhibition
TLS	Tumour Lysis Syndrome
TME	Translational Medicine Expert
TMF	Trial Master File
TMM	Team Member Medicine
TNM	Tumour, (lymph) Node, Metastasis
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
TSTAT	Trial Statistician
ULN	Upper Limit of Normal
UV	Ultraviolet
WBC	White Blood Cell count

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

The high medical need for new drugs in cancer therapy remains unchanged as still most patients with locally advanced or metastatic cancers will eventually die from the disease. The demographic development will lead to further increase in cancer incidence and the unmet need for therapy.

Several drugs targeting epigenetic modifiers have been successfully developed, including inhibitors of enzymatic "writers" such as DNA methyltransferases, and inhibitors of enzymatic "erasers" such as histone deacetylases. Modulation of the epigenetic regulators known as "readers" has recently emerged as a therapeutic strategy. One bromodomain-containing family is the BET family comprising BRD2, BRD3, BRD4 and BRDT. BET is important in regulating transcription, epigenetic memory and cell growth.

The bromodomain and extraterminal (BET) protein BRD4 recruits transcriptional regulatory complexes to acetylated chromatin, therefore facilitating the transcription of genes in areas of "open" chromatin. Pharmacological inhibition of BET proteins shows therapeutic activity in a variety of different pathologies, particularly in cancer models. These effects have been attributed to downstream target genes, whose expression is particularly sensitive to BET inhibition.

BI 894999 is an inhibitor of the BET family. The preclinical efficacy and safety profile of BI 894999 is expected to translate into a benefit for cancer patients. This study will investigate the safety and maximum tolerated dose of BI 894999, a BET inhibitor, administered orally to patients with various advanced or metastatic cancers.

[redacted]

[redacted]

1.2.1 Non Clinical Pharmacology

Molecular potency and selectivity of BI 894999
Biochemical assays were conducted to assess the inhibitory potency of BI 894999 on the protein-protein interaction of acetylated lysine and the bromodomains BRD4 BD1 and BRD4 BD2. BI 894999 inhibited the binding of bromodomain BRD4 BD1 to acetylated Histone with an IC50 of 5 ± 3 nM, of BRD4 BD2 to with an IC50 of 41 ± 30 nM.
In the BROMOscan selectivity screen, BI 894999 affected only bromodomains of the BET family (BRD2, 3, 4, T) with a constant of dissociation (Kd) of 0.49 to 1.6 nM, all the other 23 bromodomains tested showed at least 200 fold selectivity vs. BRD4 BD1. In a broader biochemical screen (from the [redacted], 71 binding assays and 25 enzymatic assays) out of all the test targets, only one receptor, the benzodiazepine receptor BZD, showed 51 % inhibition of control specific binding at a test concentration of 1 µM.

Overall, the BET inhibitor BI 894999 shows a very good selectivity profile.

Cellular Activity

The cellular potency of BI 894999 was determined in cell proliferation assays. A panel consisting of >50 acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), multiple myeloma (MM), chronic myelogenous leukaemia (CML), DLBCL (ABC and GCB-type), and T-cell lymphoma (TCL) cell lines was tested. All cell lines except the CML line K562, showed an EC50 <100 nM, with most of the cell lines displaying single digit nM EC50 values.

For solid cancer types including SCLC, mCRPC, NC, head and neck squamous cell carcinoma, neuroblastoma, medulloblastoma and glioblastoma multiforme, cell line data showed proliferation inhibitory activity of BI 894999 (c03016865-02). Proliferation inhibitory activity with BI 894999 was also recently noted in CRC cell lines in vitro (new data on file, not yet reported).

In vivo efficacy of BI 894999

The in vivo efficacy of BI 894999 was assessed in disseminated and subcutaneously engrafted xenograft models.

In lymphoma studies, the subcutaneously engrafted xenograft model TMD8 is the established routine model for DLBCL (ABC type) in C.B-17scid mice. Treatment with BI 894999 was started at a tumour size of about 70 – 100 mm^3. Compound was administered at daily oral doses of 12 mg/kg. Monotherapy of BI 894999 resulted in tumour growth inhibition (TGI) at day 20 (sacrifice of vehicle control group due to tumour size) of 89 % compared to control. Rituximab was administered intra-peritoneally (i.p.) at 1 mg/kg q3 or 4 d and resulted in TGI of 77 %. Combination of BI 894999 and rituximab resulted in TGI of 92 %.

In a second TMD8 xenograft experiment, BI 894999 treatment was combined with ibrutinib.
In this experiment BI 894999 was dosed at 8 mg/kg (daily, per os) and ibrutinib at 12 mg/kg (daily, i.p.). In this experiment, BI 894999 as monotherapy was dosed below the MTD but still resulted in TGI of 64 %. Ibrutinib dosed at the MTD resulted in TGI of 45 %. Combination of both resulted in TGI of 110% with tumour regression in 6/7 animals.

Anti-tumour activity of BI 894999 was demonstrated in patient-derived xenograft (PDX) models for SCLC in NCR-nude or NMRI-nude mice. Mice were treated at the MTD (which is different depending on the mouse strain). Three of the 12 models tested were highly sensitive to BI 894999 with TGIs between 80% and 105% and tumour regressions, whereas the other nine models show TGIs between 7% and 68%. The search for a patient selection biomarker for SCLC is ongoing.

Anti-tumour activity of BI 894999 was also demonstrated in a prostate carcinoma xenograft model (MDA-PCA-2B). Mice were treated with 5 mg/kg enzalutamide once daily or with 12 mg/kg BI 894999 once daily, with a dose reduction to 8 mg/kg on Day 12. Median tumour volume was compared with the median tumour volume in control mice. BI 894999 treatment resulted in TGI of 98%.

In the ongoing clinical study 1367.1 two responses have been documented in patients with solid tumour so far: a partial response in a patient with small bowel adenocarcinoma (treated with Schedule A) that lasted until the end of Cycle 12 and a partial response in a patient with oesophageal squamous cell carcinoma (treated with Schedule B) that lasted until the end of Cycle 6.

In summary, BI 894999 is a potent and selective BET inhibitor that showed *in vitro* and *in vivo* activity in hematological malignancies and solid tumours.

1.2.2 Pharmacokinetics and product metabolism in pre-clinical

The *in vitro* metabolism of [^{14}C] labelled BI 894999 was investigated by the use of human liver microsomes and cytosol, expressed cytochrome P450 (CYP) enzymes and flavin-containing monooxygenases (FMO) enzymes and human hepatocytes. Based on incubations with human hepatocytes and with liver microsomes at low concentrations of BI 894999 (10 µM) the contribution to hepatic oxidative metabolism of the single enzymes was estimated to approximately 50 to 60% for CYP 3A4 and to approximately 40 to 50% for FMO3 (n00240842-01)

CYP enzyme induction in human hepatocytes

The in vitro induction of CYP enzymes by BI 894999 was investigated by incubations with human hepatocytes (n00244406). Based on the results of these incubations, BI 894999 caused enzyme induction on the messenger ribonucleic acid (mRNA) level in human hepatocytes of CYP1A2, 2C8 and 3A4.
According to current most conservative cut-off criteria from the FDA (P12-05791) and EMA (P14-08681) Drug-drug interaction guidelines, BI 894999 is likely a CYP inducer if C_{max} total exceeds 0.83 nM (CYP3A4), 0.14 nM (CYP2C8) or 1.38 nM (CYP1A2).

Estimated efficacious human dose
A human clearance of 7.9 mL/min/kg was predicted based on simple allometry. A human volume of distribution at steady state of 4.9 L/kg was predicted based on mean of animal data. This resulted in a predicted human disposition mean residence time and effective half-life of 10.5 h and 7 h, respectively.

The human therapeutic dose is predicted based on effective plasma concentration in the mouse xenograft model. Assuming similar potency of BI 894999 in humans and the mouse model, and taking into account similar protein binding between both species; this translates into a therapeutic dose of 45 mg (free base) once daily to achieve an anticipated effective plasma concentration above 35 nM for 6h in humans (n00240650-01).

1.2.3 Toxicology

The toxicity profile for BI 894999 has been assessed in a 2-week exploratory study in rats, a 2-week dose range-finding study in dogs and 4-week toxicity studies in both species. In rats, a no observed adverse effect level (NOAEL) was achieved with 0.075 mg/kg. In dogs, there was no free dose down to a level of 0.0125 mg/kg. The nonclinical safety package, which also includes

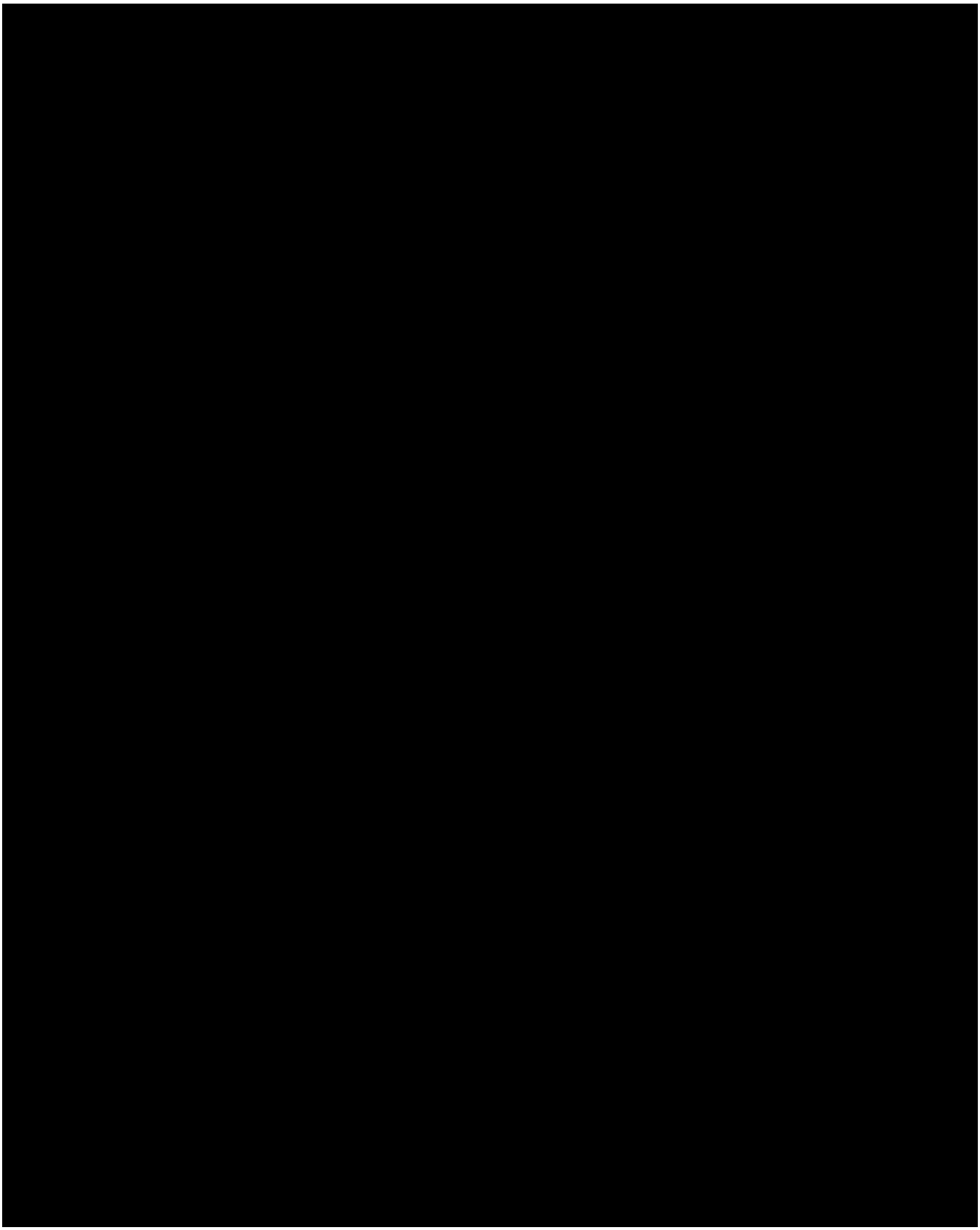
safety pharmacology and immuno-toxicology endpoints, supports the administration of BI 894999 to humans.

The primary target organs of toxicities were the lymphoid and hematopoietic system (decreases in white blood cell count, monocytes, lymphocytes and platelet counts), the digestive tract (oral mucositis, degeneration, erosion and ulcers), the liver (hepatocellular atrophy, changes in liver enzymes), the testes (germ cell degeneration and loss) and the kidneys. Inhibition of the BET proteins with BI 894999 showed a rather steep dose-adverse effect curve and a delayed onset of adverse effects.
The assessment of the photochemical properties of BI 894999 indicates a potential risk of photo-toxicity. Appropriate protective measures must be taken during outpatient trials.
No cardio-toxicity risk is expected based on pre-clinical toxicity data.

A safe starting dose was estimated in accordance with the General Guide for Starting Dose Selection for a Cytotoxic Agent in Cancer Patients (FDA/CDER) and based on the data of 4-week toxicity studies in rats and dogs. Using the conversion factor of 6, the high dose of the rat study of 0.5 mg/kg (severely toxic dose for 10 % of rodents, STD10) was transformed to 3 mg/m². The high dose of the dog study (non-severely toxic dose) was converted from 0.05 mg/kg to 1 mg/m² using the conversion factor of 20. The dog was considered to be the most sensitive species. Following the recommended decision tree 1/6 of 1 mg/m² = 0.17 mg/m² is the safe starting dose for cancer patients, which corresponds to 0.0045 mg/kg (using the conversion factor of 37). Based on a patient body weight of 70 kg, the calculated starting dose would be 0.31 mg/patient/day. However, due to the availability of tablet dose strengths, the starting dose in this first-in-human Phase I trial will actually be 0.2 mg per patient per day for the very first patient included in the trial, in Schedule A.

In summary, based on preclinical safety pharmacology studies, side effects of BI 894999 in humans may include symptoms related to the lymphoid and hematopoietic system (decreases in white blood cell count, monocytes, lymphocytes and platelet counts), the digestive tract (oral mucositis, diarrhoea,), liver (liver enzymes), kidneys and blood glucose levels. Patients will therefore be monitored for these side effects. Based on current knowledge of BET inhibitors and non-clinical data obtained for BI 894999, effects on testes are anticipated.

[redacted]



2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Most patients with locally advanced or metastatic tumours will succumb to their disease. Thus, there is a substantial need for novel therapeutic strategies to improve the outcome for patients with advanced or metastatic malignancies. This is particularly true for patients with NC which is a very aggressive malignancy for which no standard of care has been established. As this rare disease is observed in adolescents and young adults (R18-2451), for this indication, the trial will allow inclusion of minor patients aged 15 years or more.

Recently, preliminary data of the Phase I trials of other BET inhibitors have been reported and promising results were observed in patients with lymphoma particularly in DLBCL. In the Phase I trial of CPI-0610 in patients with relapsed/refractory lymphoma, objective responses were observed in 4 patients with lymphoma including 3 patients with DLBCL (R16-1012). In the Phase I trial of OTX015 in patients with advanced haematological malignancies, 3 patients in the DLBCL cohort experienced an objective response (R15-1329).

BI 894999 is a potent inhibitor of BET bromodomain and as such prevents the transcription of relevant, as yet unidentified genes and thereby blocks proliferation and induces apoptosis in cancer cells (data on file).
Based on the preclinical studies [redacted], the observed anti-tumour activity in preclinical studies of BI 894999 and in clinical studies of other BET inhibitors and safety profile of BI 894999, clinical testing of BI 894999 is warranted. The present study is the first-in-human study to determine the safety profile and the MTD of BI 894999 in cancer patients for whom no standard treatment options exist.

2.2 TRIAL OBJECTIVES

The main objective of the dose escalation part of the trial is to determine the MTD using a continuous dosing Schedule A , the MTD using an intermittent Schedule B (2 weeks on, one week off in 3-week cycles) and the MTD using an intermittent Schedule C (a loading dose on first day followed by a maintenance dose for the next six days and followed by one week off treatment, repeated every two weeks in 4-week cycles) in patients with solid tumours and provide safety data in terms of drug-related adverse events (AEs) for the recommendation of the dose and schedule of treatment for the expansion Phase Ib of this trial (between Schedules A and B) and for further trials in the development of BI 894999 (between Schedules B and C) (see Section 5.2). Once the MTD has been determined for both schedules A and B in patients with solid tumours, the MTD was determined as well in patients with diffuse large B-cell lymphoma (DLBCL), using the DMC recommended schedule for solid tumours which was Schedule B. The MTD will also be determined in patients with DLBCL using the Schedule C in order to recommend the dose and schedule for further trials in DLBCL in the development of BI 894999 (see Section 1.3).

Secondary [redacted] objectives are the determination of the pharmacokinetic (PK) profile of BI 894999 after single and multiple dose (see Section 5.4), [redacted]) and assessment of anti-tumour activity (see Section 5.2).

In the expansion phase, the main objective lies upon collection of further safety information at the dose recommended by the data monitoring committee (DMC) for Phase Ib (2.5 mg in Schedule B was recommended based on Schedule A and B data) and with the Schedule (between B and C) and dose recommended by the DMC for the Phase Ib NC cohort. The secondary [redacted] objectives will be to increase the number of patients with solid tumours and with evaluable PK results at the recommended Phase Ib dose for Schedule B in the four types of tumours and for Schedule C in the NC cohort, and the same as in the dose escalation part for the assessment of anti-tumour activity.
[redacted]

2.3 BENEFIT - RISK ASSESSMENT

BI 894999 inhibits tumour growth and induces tumour regression in pre-clinical models. Based on pre-clinical results, the inhibitory effects on BET bromodomain may translate into a clinical benefit in cancer patients. Although the starting dose is not expected to be efficacious, the dose escalation scheme guided by a Bayesian two-parameter logistic regression model (BLRM) (de-escalation of dose is possible in case of insufficient tolerability of a dose level) is designed to escalate the dose quickly into a dose range where efficacy may be seen while still minimizing the risk of undue tolerability issues.

None of the doses tested in dogs were free of adverse effects. Based on these studies, the most relevant side effect of BI 894999 is expected to be a transient inhibition of proliferation of normal dividing cells in mucosal tissue and bone marrow. Inhibition of mucosal proliferation may lead to gastro-intestinal symptoms such as nausea, diarrhoea, mucositis, and/or abdominal pain. Patients in this study will be closely monitored for these side effects and supportive treatment will be given by the investigators if necessary. The side effects on bone marrow cells may lead to a temporary decrease of blood cells and platelets. These side effects are frequently seen in cancer patients treated with conventional cytotoxics or targeted therapies and can readily be monitored with regular blood tests. Supportive treatment for some of these effects is available.

In addition to these effects, some changes in laboratory values were observed such as an increased level of glucose and a decrease of phosphate.
Specific procedures have been implemented to early detect these and other potential side effects and to allow their immediate supportive treatment and follow up. The sites will be experienced Phase I oncology sites with the appropriate clinical personnel available and access to emergency care units in case of need. The patients will also remain at the clinical site, under surveillance, for the first 24 hours after the very first administration.

Preclinical studies with BI 894999 have also shown degeneration of germ cells in testes of dogs. This is the reason why male patients having a partner of childbearing potential must use condoms and ensure their partner is using a highly effective method of birth control during the trial and for at least three months after the end of the trial.

In the study of the effect on hERG-mediated potassium current, BI 894999 did not show any *in vitro* signal for a pro-arrhythmic risk based on prolongation of ventricular repolarisation. This was confirmed in studies in dogs and rats which did not show a negative effect on myocardial contractility or a pro-arrhythmic effect (c03016865-02). However, to confirm this absence of pro-arrhythmic effect in humans, in addition to normal clinical monitoring of the cardiovascular functions by measurement of pulse and blood pressure (BP), regular electrocardiogram (ECG) records will be performed for further characterisation and will be centrally analysed by a core lab.
On 04 Oct 2016, the sponsor decided to put a temporary hold on further recruitment of patients in trial 1367.1. The measure was taken since review of patient data revealed some patients with increased troponin levels. A thorough review by cardiologists was initiated with regards to troponin levels, ECG, and clinical summaries of all enrolled patients. Evidence supporting a causal association between the increased laboratory troponin values and the administration of the trial medication could not be established. There were no corresponding clinically significant findings based on the reviewed ECGs and the clinical summaries of enrolled patients. The external review concluded that the cause of troponin elevation may be multifactorial in the trial patient population. In conclusion, the findings were considered to not preclude further clinical development. Consequently, patient recruitment was re-started.

Patients on study will be closely monitored and will undergo regular controls of CK and troponin highly sensitive (see Section 5.3.3), together with ECG evaluation.
Furthermore, every patient will undergo a mandatory echocardiography or multiple gated acquisition (MUGA) scan for left ventricular ejection fraction (LVEF) determination during screening and then at the end of Cycle 2 and at the end of treatment (if the patient's condition at the time of end of treatment permits so). Cardiologic assessments (CK, troponin hs (T or I), ECG, echocardiography and any other examination as judged necessary) should be prompted by the investigator upon clinical indication at any time (see Section 4.1.4.3.1).

Other treatment-emergent AEs which were most frequently observed in this Phase I trial so far include: fatigue, thrombocytopenia, decreased appetite, dysgeusia, increased CK, diarrhoea, nausea and stomatitis. Neutropenia was also observed but it was less frequent than the above AEs.

Thrombocytopenia is considered an expected AE associated with BI 894999. Thrombocytopenia (especially CTCAE grade 4) could be associated with an increased risk of bleeding and is therefore considered medically important.

Asymptomatic grade 1–2 factor VII decrease was noted in some patients treated with another BETi, OTX-015 in a Phase I study conducted in patients with lymphoma or multiple myeloma (R15-1329). Prolonged coagulation times have also been reported as treatment related adverse events in a Phase I study with the BET inhibitor INCB057643 (R18-1831) and in a Phase I

Study with the BET inhibitor GSK525762 (R18-2390). Monitoring of coagulation parameters in the 1367.1 study revealed that some patients present with mild prolongation of prothrombin time (PT) and increase in international normalized ratio (INR) on Day 14 of Cycle 1. Coagulation parameters will continue to be monitored during the study and will be evaluated before the performance of tumour biopsies. Tumour biopsies will only be performed if the platelet count is above 50 000/mm^3 without the support of transfusion and coagulation parameters (aPTT, PT in sec and INR) are within normal limits on the day of the biopsy. It is possible that prolonged PT will occur concurrently with thrombocytopenia in a patient being treated with BI 894999. The coexistence of thrombocytopenia and coagulopathy could potentially increase the risk of bleeding events. In order to reduce the risk of bleeding events in patients with severe thrombocytopenia and prolonged coagulation times, mandatory prophylactic platelet transfusions need to be administered to all patients who present with a platelet count below 20 000/mm^3.

Based upon a non-clinical safety study *in vitro*, a potential risk of photo-toxicity / photosensitization *in vivo* could not be excluded. Therefore, adequate precautions must be taken during treatment with BI 894999 (avoidance of prolonged ultraviolet (UV) exposure, use of broad spectrum sunscreen).

Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients' safety (see also Section 5.3.6.1).

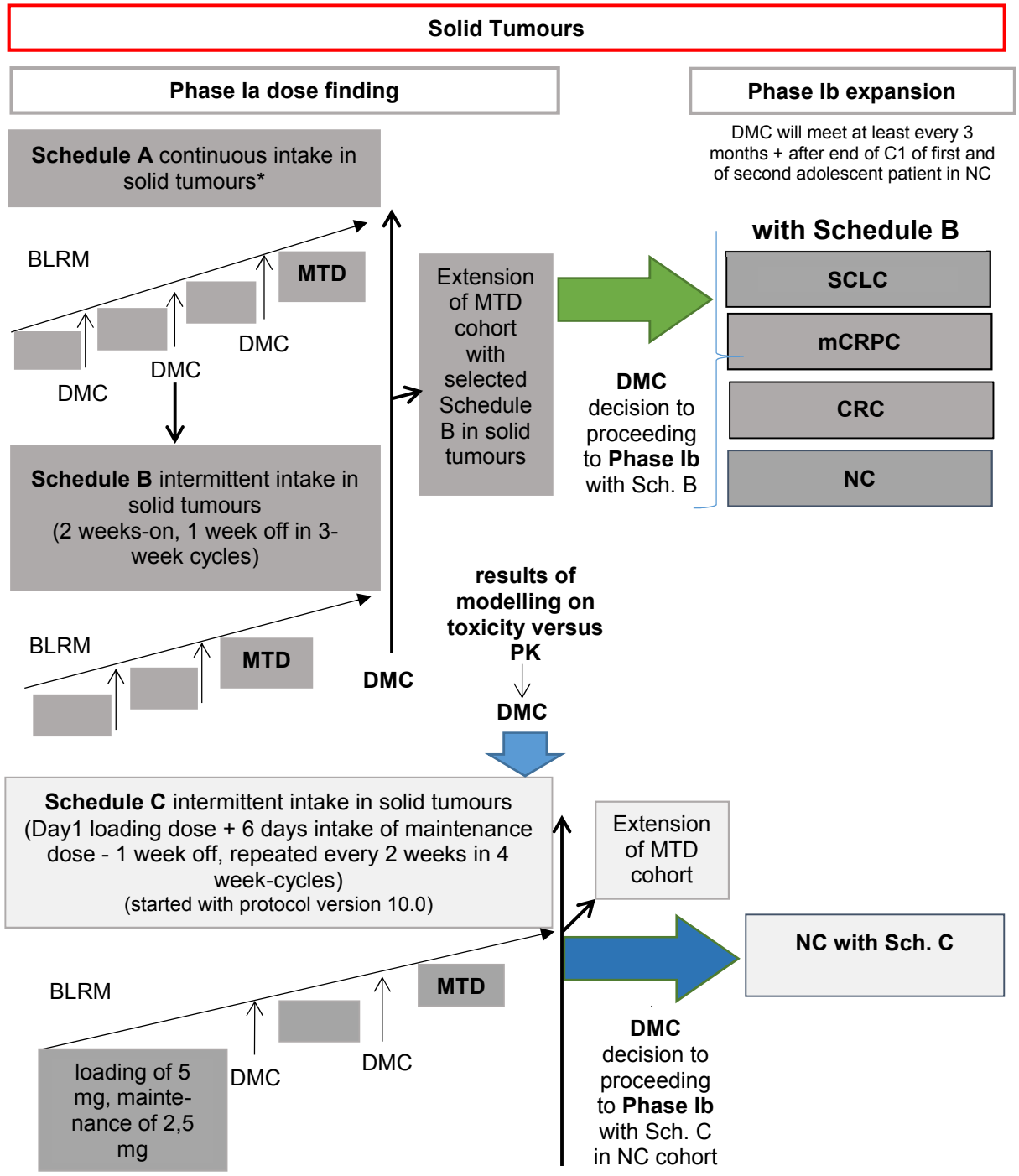
Based on its mode of action, BI 894999 is not expected to have a relevant impact on susceptibility to or on the course of an infection, however, in DLBCL patients, the susceptibility to a COVID-19 infection may be increased.
Patients in this trial may have an increased risk for severe illness from COVID-19. In case of an increased risk of COVID-19 infection, physical visits to the sites should be avoided where the investigator judges that this is the safest course of action. They should be replaced with remote visits, procedures and lab testing will be done remotely as far as possible (see Sections 4.1.4.2 and 6.1). These measures ensure the safety of the patients throughout the trial, maintain the integrity of the trial and will not affect the benefit-risk of BI 894999.
In case of a confirmed infection, trial treatment will be interrupted immediately and appropriate measures for monitoring, treatment and quarantine will be implemented. The patient may resume treatment following recovery from a COVID-19 infection if the patient is expected to derive clinical benefit, as agreed between the Investigator and Sponsor.
Trial procedures such as blood sampling, imaging with e.g. contrast media, tumour biopsies, are part of standard of care in these advanced cancer patients but are performed at a higher frequency during this trial. The additional blood samplings increase the risk for anaemia which can be corrected by appropriate transfusion if necessary. The imaging performed every other cycle can bring additional long term radiation burden but these advanced patients are not expected to remain for very long periods in the study and it is the only way to detect early progression or early response to avoid unnecessary further treatment or a premature stop while the trial treatment would be beneficial to the patient.

There is an added risk for pain, swelling, bleeding for those patients who will undergo tumour biopsies at screening and during the trial, under treatment. For this reason, biopsies will only be performed when deemed safe by the investigator, if the platelet count is at least 50 000/mm^3 without the support of transfusion and if coagulation parameters are within normal limits on the day of the biopsy.

Patients with advanced solid tumours, and relapsed/refractory DLBCL who have limited or no established treatment options may theoretically benefit from the treatment with BI 894999 (tumour regression, disease stabilisation or improvement of tumour-related symptoms). The potential benefit of therapy with BI 894999 is expected to outweigh the treatment and procedures related risks.
For the NUT carcinoma patients of Phase Ib, enrolment of adolescents ≥15 years of age will be allowed. Indeed, the dose, safety and metabolism in adolescents of ≥15 years are expected to be similar to adults because body size is expected to be close to adults and organ maturation is expected to be completed. However, to confirm the hypothesis that safety is similar in adolescents and adults, a mandatory DMC meeting will take place after the first and after the second adolescent patient completes Cycle 1 to assess whether the adult dose is tolerable in adolescents. In this population the benefit is expected to outweigh the risks because there is no standard treatment available and BI 894999 is specifically targeting the NUT fusion that is characteristic for the disease.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN



*dark boxes show completed steps at the time of protocol version 12.0

Figure 3.1: 1: Trial Design for Solid Tumours

DLBCL in Phase Ia dose finding

*dark boxes show completed steps at the time of protocol version 12.0
** DMC made the decision on MTD in Sch. B after protocol version 11.0 approval and before start of Sch. C dose finding part

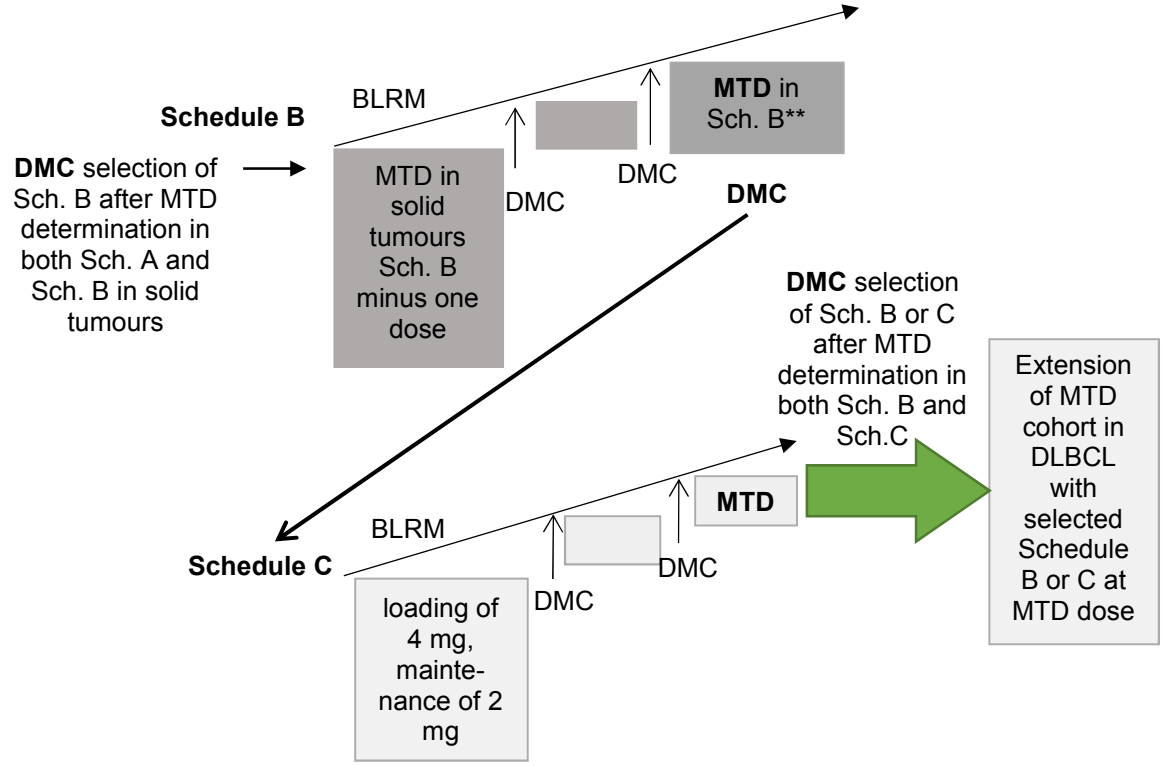


Figure 3.1: 2: Trial Design for DLBCL

The trial is designed as an open label, uncontrolled study and had a dose escalation Phase Ia to determine the MTD in solid tumours in two different schedules, Schedule A with continuous dosing once daily in 3-week cycles and Schedule B with once daily dosing for 2 weeks followed by one week off treatment in 3-week cycles with an extended cohort at MTD in the selected schedule B) as decided by the DMC in December 2017, based on the safety, pharmacokinetic and pharmacodynamics data available from all patients treated by that stage. This is then followed by an expansion Phase Ib in selected solid tumour indications with the chosen dose (2.5 mg) and schedule (Schedule B) as decided by the DMC in April 2018. The DMC also confirmed the decision on which types of tumours to include in this expansion phase (DMC meeting of September 2017). During the Phase Ia, once the MTD has been determined in both Schedules A and B in solid tumours, testing of the chosen Schedule by the DMC (i.e. Schedule B) in patients with DLBCL commenced to determine the MTD of BI 894999 with Schedule B in patients with DLBCL. The starting dose was one dose lower than the MTD dose in patients with solid tumours.

The dose escalation part using Schedule B in patients with solid tumours happened in parallel with the dose escalation part of Schedule A and started at the highest dose level tested in Schedule A in solid tumours considered to be safe by the DMC.

Further to the results from modelling of toxicity observed on thrombocytes and results of PK and pharmacodynamics, an additional dose escalation was performed with a Schedule C with the aim of finding an optimal dosing schedule (loading dose on Day 1 followed by 6 days of maintenance dose and one week off treatment, repeated every 2 weeks in 4-week cycles) in parallel with the dose finding part in DLBCL patients with Schedule B. The starting maintenance dose for Schedule C was the dose selected by the DMC for Schedule B in Phase Ib which is 2.5 mg with a double loading dose of 5 mg. In parallel, after approval of protocol version 11.0, the MTD will also be determined for Schedule C in patients with DLBCL, starting at one dose tier below the one used in solid tumours to start with Schedule C, both for the loading dose and for the maintenance dose, meaning with a loading dose of 4 mg and a maintenance dose of 2 mg. Once the MTD with both Schedules B and C in DLBCL patients have been determined, the DLBCL cohort will be extended at the MTD level of the schedule selected by the DMC to have the best toxicity profile, to include in total for the MTD cohort from 12 to 14 patients.

The dose escalation will be guided by a BLRM (see the different scenarios in Appendix 10.3) (de-escalation of dose is possible in case of insufficient tolerability of a dose level) (R04-0569), and will be determined by the DMC which will evaluate and decide on the dose to be administered for the next cohort. An escalation with overdose control design will increase the chance of treating patients at efficacious doses while reducing the risk of overdosing.

Dose escalation Phase Ia of Schedule A in patients with solid tumour:
One patient was treated per dose cohort until a first drug-related AE of CTCAE grade ≥ 2 occurred during the first treatment cycle (see description in Section 4.1.3.1). Thus, the next patient could only start the treatment at the next dose level once it was confirmed that the previous patient from the lower dose level did not experience a drug-related CTCAE grade ≥ 2 AE during Cycle 1.

In case no patient from the first cohort experienced a CTCAE ≥ grade 2 drug-related AE during Cycle 1, the dose could be increased from 0.2 mg to 1 mg in the second cohort. In case no patient from the second cohort experienced a CTCAE ≥ grade 2 drug-related AE during Cycle 1, the dose could be increased from 1 mg to 5 mg in the third cohort. Afterwards, increments have followed the Bayesian model as explained in Appendix 10.3.

If a patient, in a single patient cohort, experienced a CTCAE grade ≥ 2 drug-related AE during Cycle 1 at any dose level, additional patients were to be entered in the same cohort and at least 2 patients evaluable for dose limiting toxicity (DLT) in Cycle 1 were required per cohort, from that cohort onwards.

The second patient of a same cohort could only start his treatment after the first patient of the cohort had been observed for a period of 7 days of treatment and a second and a third patient could then be started at the same time.

In case only 2 patients were evaluable and neither had experienced a dose-limiting toxicity within the first cycle (21 days), then dose-escalation could occur based on these 2 patients. But, if one of these 2 patients experienced a DLT in the first cycle (21 days), a third patient had to be enrolled at the same dose level and be evaluable for DLT in the first cycle.

After all patients in a cohort had either experienced a DLT or had been observed for at least one cycle without a DLT (until Day 22 of Cycle 1), the BLRM was updated with the newly accumulated data. The overdose risk was then calculated for each dose, and escalation was permitted to all doses, which fulfilled the Escalation with Overdose Control (EWOC) criterion and dose escalation rules according to Section 4.1.3. Decision on next step (dose escalation, de-escalation or cohort extension) was made by the DMC, based on the collected safety data as well as other data (e.g., PK / pharmacodynamics data) when available.

If DLTs were observed in the first two consecutive patients of a previously untested dose level, subsequent enrolment to that cohort was stopped. The BLRM was re-run to confirm that the dose-level still fulfilled the EWOC criterion. The DMC decided whether the next patients were to be enrolled at the same dose level, or if they were to be enrolled to a lower dose level. Figure 3.1: 3 shows how the decision of dose escalation was made.

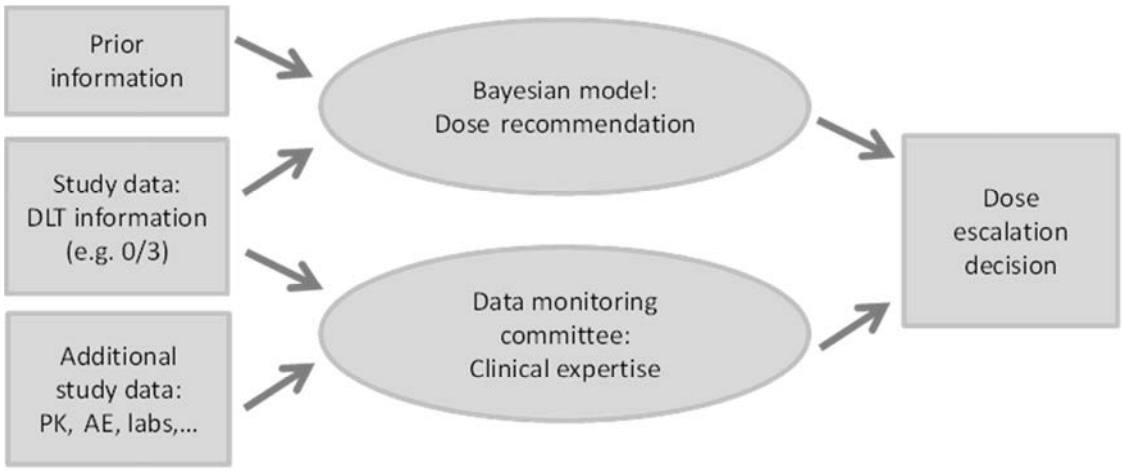


Figure 3.1: 3: Escalation Decision – Combination of clinical and statistical expertise

Dose escalation Phase Ia and expansion Phase Ib of Schedule B in patients with solid tumour:
The starting dose for the dose escalation Phase Ia of Schedule B in patients with solid tumour was the highest dose level tested in Schedule A in solid tumours considered to be safe by the DMC. Dose escalation and de-escalation was guided by the BLRM from the beginning, i.e., no single patient cohorts were foreseen.

The DMC could recommend stopping the dose escalation phase after the criterion for MTD was fulfilled.

Once the MTD had been determined for both Schedules A and B in patients with solid tumours, the DMC made a recommendation on the recommended Schedule based on safety, PK and pharmacodynamics data available from all patients treated at this stage, and the MTD cohort of the chosen schedule which was Schedule B was further extended to enrol a total of 12 patients with solid tumour at this dose level of 2.5 mg.

At doses deemed close to the MTD in Schedule A in patients with solid tumours (decision was made by DMC on which cohort(s) the [redacted] study would happen) and at the MTD dose in patients with solid tumours, a minimum of 12 patients and up to 20 patients in total with solid tumours in either Schedule A or B participated to the determination of [redacted] on pharmacokinetics (see Section 10.2.2).

Once the MTD was determined for both Schedules A and B in solid tumours and the choice of the most appropriate Schedule was made (Schedule B), newly recruited patients in the extension of the MTD cohort could undergo optional tumour biopsies at screening and at steady state in Cycle 1.
In Phase Ib, the tumour biopsies at baseline and at steady state (between Day 8 and Day 11) under treatment in Cycle 1 were mandatory. The baseline biopsy could be replaced by sending of tumour archival tissue from the latest relapse if not older than 6 months. A 2-3 mL EDTA blood DNA sample was mandatory, once, at any time, for all patients undergoing a tumour biopsy or for whom archival tumour tissue is sent.
For the biopsy to be allowed, platelet count and coagulation have to be checked prior to each biopsy and have to be adequate, meaning platelets of at least 50 000/mm^3 without the support of transfusion and coagulation parameters within normal limits.
Should the biopsy under study treatment, between Day 8 and Day 11 of Cycle 1 not be feasible in 5 out of the first 20 patients of Phase Ib in solid tumours because of abnormal coagulation parameters and/or a platelet count below 50 000/mm^3, the timing of biopsy at steady state would be moved ahead, between Day 3 and Day 8 for the next patients.
The tumour biopsies in Phase Ib were however not requested for mCRPC patients with only bone lesions and for patients with therapeutic INR because of treatment with a vitamin K antagonist or a novel oral anticoagulant. Biopsies remained optional for NC patients.
The on treatment biopsy could remain optional if no easily accessible lesions were available.

Dose escalation Phase Ia with Schedule C in patients with solid tumours:
The starting dose for the dose escalation Phase Ia of Schedule C in patients with solid tumour was the MTD determined for Schedule B, which is 2.5 mg with a loading dose of 5 mg. So the patients took 5 mg on Day 1 followed by 2.5 mg from Day 2 till Day 7, then a week off treatment and again a loading dose of 5 mg on Day 15 followed by a maintenance dose of 2.5 mg from Day 16 till Day 21, then a week off treatment in 4-week cycles. Dose escalation and de-escalation for subsequent cohorts was guided by the BLRM for this schedule.

The DMC could recommend stopping the dose escalation phase after the criterion for MTD was fulfilled (see Section 7.1).
Once the MTD has been determined for Schedule C in patients with solid tumours, the MTD cohort will be further extended to enrol a total of 12 patients with solid tumour at this dose level.

Dose escalation Phase Ia of selected schedule (B) in patients with DLBCL:
Once the MTD was determined for both Schedules A and B in solid tumours and the choice of the most appropriate Schedule was made (Schedule B), the dose escalation started with this Schedule (B) in patients with DLBCL.

The starting dose for the dose escalation in patients with DLBCL (2 mg) was one dose level below the MTD of the selected schedule (B) in patients with solid tumour and the dose escalation and de-escalation was guided by the BLRM from the beginning, i.e., no single patient cohorts were foreseen.

Dose escalation Phase Ia of Schedule C in patients with DLBCL:
After MTD determination for Schedule B in DLBCL patients, a dose escalation was started with Schedule C in patients with DLBCL.
The doses to use in the first cohort for the dose escalation Phase Ia of Schedule C in patients with DLBCL were, both for the loading and the maintenance dose, one dose tier below the doses used for the first cohort with Schedule C in patients with solid tumours. So the patients take 4 mg on Day 1 followed by 2 mg from Day 2 till Day 7, then a week off treatment and again a loading dose of 4 mg on Day 15 followed by a maintenance dose of 2 mg from Day 16 till Day 21, then a week off treatment in 4-week cycles. Dose escalation and de-escalation for subsequent cohorts will be guided by the BLRM for this schedule.

Once the MTD will be determined in both Schedules B and C in patients with DLBCL, the DMC will make a recommendation on the schedule to be selected between B and C to further expand the MTD cohort in DLBCL in 6 to 8 additional patients.

In addition, patients (with solid tumour or DLBCL) who are responding to treatment or who are benefiting from treatment, may undergo optional fresh tumour biopsy (platelet count and coagulation must be checked prior to each biopsy and must be adequate, see above) and may provide optional consent for analysis of their archival tumour sample. In these patients who provide consent for a fresh tumour biopsy and/or analysis of their archival tumour sample, a 2-3 mL EDTA blood DNA sample is mandatory.

The observation period for DLT is 21 days of the first cycle only (to be assessed at Day 22)) in Schedules A and B. For Schedule C, the observation period for DLT is 28 days of the first cycle (to be assessed on Day 29).
However, confirmation of the recommended dose for the Phase Ib expansion part was made by the DMC, based on all available safety, PK and pharmacodynamics data at all treatment cycles, at the time of decision in April 2017. The DMC in addition made recommendation on the types of solid tumours that were chosen for the Phase Ib part, based on anti-tumour signals that appeared from data collected during the escalation part, together with additional pre-clinical data available at the time of the end of the escalation phase.

The expansion Phase Ib with Schedule B recruited a minimum of 9 evaluable patients (for PK and response by RECIST at the end of Cycle 2 or by bone scan and PSA at the end of Cycle 4 in mCRPC patients with non-measurable disease by RECIST 1.1) and a maximum of 20 evaluable patients with measurable (or non-measurable per RECIST 1.1 for mCRPC patients) and progressive disease, per type of tumours selected by the DMC: SCLC, mCRPC, CRC and NC. For the NC cohort, since this is a rare disease, the number of patients was not pre-defined but tended to include up to a maximum of 40 patients.
Once the MTD for Schedule C was determined in Phase Ia in patients with solid tumours, the DMC recommended the best schedule between B or C to further recruit patients in the NC

cohort. As Schedule C was selected, a Schedule C NC cohort was opened to recruitment for up to a maximum of 40 patients while the NC cohort with Schedule B was closed to recruitment.

This expansion phase will further evaluate the safety including re-evaluation of the recommended Phase II dose and the selected schedule (B or C), efficacy, pharmacokinetic and biomarker profile of BI 894999 in patients with the chosen specific types of tumours. The DMC will have regular meetings (at least once every 3 months) to evaluate the safety of the patients in Phase Ib and confirm the safety of the selected dose in the specific patients' population. In addition, the DMC will have meetings after the first and after the second adolescent patient with NC finishes the first cycle to assess whether the adult dose is tolerable in adolescents.

Patients will be kept at the institution, based on convenience for the patient and the investigator's decision of patient's need for safety surveillance, for the first administration of study medication, for a period of 24h from C1D1 until C1D2 (at investigator's discretion, can be limited to a period of 4h on Day 1 in DLBCL and NC patients recruited after approval of protocol version 12.0) and for 48h in the [redacted] cohort until drug administration of C1Day3. Patients will be kept at the institution for a period of 24h, from C1D14 until last PK sample of Day 15 for Schedules A and B (24h post-dose of Day 14 dose in Schedule A or 32h post-dose of Day 14 in Schedule B), based on convenience for the patient and investigator's decision. For Schedule C, this will be on C1D21 until last PK sample of Day 22. However, all other visits from first cycle and all visits from subsequent cycles will be performed in an outpatient setting except if medically or operationally justified, at the discretion of the investigator. During treatment, the investigator will determine the safety parameters, record the AEs and perform additional investigations as outlined in the Flow Chart.

A clinical disease assessment will be performed after every treatment cycle and a tumour response assessment by imaging every other cycle for all patients with solid tumours. The type of imaging (computed tomography (CT) scan or magnetic resonance imaging (MRI), with or without contrast media) is left to the decision of the investigator but must be the same all over the trial period and must allow for evaluation according to RECIST 1.1. Assessment of response will be performed at the investigator's site and will be sufficient for the decision whether the patient will continue therapy according to the criteria specified in Section 4.1.4. In mCRPC patients without a measurable disease via RECIST 1.1, the response assessment had to be performed on bone scan every 12 weeks coupled with PSA level at the same time-point as imaging. In patients with DLBCL, the response assessment will be performed by imaging via FDG-PET/CT scan after end of Cycle 2, of Cycle 4 and every four cycles thereafter.
Patients with a clinical benefit after a cycle of BI 894999 (absence of disease progression (except for NC patients for whom the investigator judges that there is clinical benefit and for whom no other treatment option is available) and good treatment tolerance) and who have recovered from any clinically or haematologically relevant drug-related AE of grade 3 or 4 (to grade 1 or less or to baseline grade, except grade 2 peripheral sensory neuropathy as well as anaemia, lymphopenia), as judged by the investigator, are eligible for a further treatment cycle.

Intra-patient dose escalation will not be allowed as well as switch from one schedule to another. Patients included in the escalation phase are not eligible to enter the expansion phase.

Patients experiencing DLT or any drug related significant AE necessitating a dose reduction according to investigator's judgement are eligible for further treatment cycles with BI 894999 at one dose tier below in the same schedule, as soon as recovery from drug related toxicities allows further treatment. For Schedule C, this means a decrease of the loading dose in steps of 1 mg and of the maintenance dose in steps of 0.5 (e. g., for the first cohort, the loading dose would be reduced from 5 mg to 4 mg, from 4 mg to 3 mg, from 3 mg to 2 mg while the maintenance dose would be decreased from 2.5 mg to 2 mg, from 2 mg to 1.5 mg, from 1.5 mg to 1 mg). Once a dose reduction occurred, the patient must continue at the reduced dose and may not be re-escalated later on. A patient may decrease the dose each time as necessary during the trial to the next lower dose level tested (or as explained above for Schedule C) because of DLT occurrence but not below a dose of 1 mg (maintenance dose in Schedule C).

Patients eligible for a further (repeat) treatment cycle will not start before 22 days after the start of the previous cycle for Schedules A and B, not before 29 days after the start of previous cycle for Schedule C.

If a patient has to be discontinued from the trial treatment, the end of treatment (EOT) visit with all necessary assessments as described in Sections 6.2.3 and 10.5.3 must be performed as soon as possible once the decision is taken. Follow-up visits will be performed after the EOT visit until progression of disease, death, treatment with any other anti-tumour therapy, lost to follow-up (every attempt must be made to avoid this option, e.g. by phone contact with the patient or relatives) or until the end of the trial. For the NC patients, the vital status will continue to be collected until death, loss to follow-up, withdrawal of consent to be further followed-up or until 12 months after the end of the whole trial, to be able to determine the overall survival in this population, according to their informed consent. Ongoing AEs must also be followed up until resolution or until the investigator deems it is no longer necessary to follow them up. The first follow-up visit which is the end of residual effect period (EOR) visit must be performed 30 days (+7 days) after the EOT and subsequent follow-ups, if applicable, at 12 weeks intervals or earlier if appropriate. Follow-up visits may also be performed by telephone interview in case the patient is unable to visit the investigator.

The trial will end when the last ongoing patient has completed the EOT visit and the EOR visit.

3.1.1 Administrative structure of the trial

Boehringer Ingelheim (BI) is the sponsor of this trial and it was planned to start the trial in 2 centres specialized in the treatment of advanced cancers and experienced in Phase I studies in oncology, in one country. More centres from the same country and from additional countries were initiated. However, Schedule C escalation part in patients with solid tumours only happens in the participating sites in Belgium.

A Coordinating Investigator was nominated by BI from one of the trial participating investigators and is responsible to coordinate investigators at different centres participating in this multicentre trial. Tasks and responsibilities, including the final signature of the clinical trial report (CTR), are defined in a contract. Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, are filed in the trial master file (TMF).

BI has appointed a Trial Clinical Monitor (TCM), responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal standard operation procedures (SOPs),
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- order the materials as needed for the trial,
- ensure appropriate training and information of local clinical monitors (CMLs), Clinical Research Associates (CRAs), and Investigators of participating countries.

A DMC was appointed for Phase Ia to evaluate DLTs, overall safety and other available data (e.g. PK data) and confirm dose escalation steps in the three Schedules A, B and C in patients with solid tumours. Once the MTD was determined for both Schedules A and B in solid tumours, the DMC recommended a Schedule to use in the MTD extension cohort in patients with solid tumours as well as for determination of MTD in patients with DLBCL. Schedule B was selected. After decision in protocol version 11.0 to also test Schedule C for MTD determination in DLBCL patients, once MTD will be determined for both Schedules B and C in this patient population, the DMC will recommend a Schedule to use in the MTD extension cohort in patients with DLBCL.

The DMC also evaluated all available data to confirm the proceeding to Phase Ib expansion, the recommended Phase Ib dose (2.5 mg) and schedule (Schedule B) in patients with solid tumours as well as the decision for the types of tumours in this expansion Phase Ib.
Once the MTD was determined for Schedule C in solid tumours patients, the DMC made the recommendation for continuing the recruitment in the NC cohort of Phase Ib with Schedule C. The recruitment to the NC cohort with Schedule B was closed.

Members of this DMC are the Principal Investigators (PIs) of the participating trial sites, the Team Member Medicine (TMM), the TCM, the trial statistician (TSTAT), the Trial Pharmacokineticist (TCPK) and the Translational Medicine Expert (TME) or their delegates. The extended membership is described in the DMC charter.

During DMC meetings, the information on the overdose risk are presented by the BI trial team. Additional information, such as lower grade AEs, PK (when available), pharmacodynamics biomarkers (when available), individual patient profiles and other relevant information such as the outcome events of progressive disease not reported as (S)AEs are also presented. Based on this information, the members of the DMC reach a joint decision on the next dose level to be investigated. This dose level may be above, below or identical to the currently investigated dose level. The DMC also recommends the size for the next cohort (minimum one, maximum six patients per cohort, until MTD where up to 12 patients will be included, for the chosen Schedule between A and B, which was Schedule B, for Schedule C in patients with solid tumours and in patients with DLBCL). The final decision on the next cohort size is however made by a mutual decision between the TMM and the Coordinating Investigator. [redacted]

Minimum needed data for dose escalation decision is detailed in a DMC charter that is filed in the TMF. Minutes of the DMC meetings and recommendations are documented and archived by the TCM in the TMF.
During Phase Ib, the DMC will also regularly review the safety and efficacy data of patients entered in the specific cohorts. In the NC cohort, the DMC will specifically evaluate safety data of the first cycle in the first and second adolescent included in the cohort to assess whether the adult dose is tolerable in adolescents.

Once the primary endpoint of the Phase Ia was reached in patients with solid tumours for both Schedules A and B and the MTD was confirmed in the extension cohort with the most appropriate schedule in these patients (Schedule B was selected), the Phase Ib started and a Phase Ia safety analysis report was prepared based on the Phase Ia data for Schedules A and B in patients with solid tumours. A summary of safety and efficacy endpoints and determination of the recommended Phase Ib dose and schedule was included in the Phase Ia safety analysis report. The Phase Ia report is made available for all investigators who participate in the Phase Ib. This report is also sent to regulatory agencies. It will be the basis, together with the Schedule C results in patients with solid tumours, for publication of Phase Ia results of patients with solid tumours by the Coordinating Investigator.

The safety laboratory investigations are performed at the investigator's site (see 5.3.3), as well as ECGs. In addition, all ECGs are analysed by a central laboratory (in case of clinically relevant abnormalities, the investigator will be notified by email and/or fax by the central laboratory).
Analyses of pharmacokinetics samples are performed by BI.

[redacted]

Further details on CROs for samples handling, shipments and analyses are given in the ISF/laboratory manual.

The trial drug is directly forwarded by Boehringer Ingelheim or via a distributing CRO to the investigator's pharmacy where it will be stored according to storing requirements as described in the pharmacy manual. The pharmacist (or investigator directly to the patient, where legally authorised) will deliver the necessary amount for an individual patient to the investigator upon his/her request, according to the procedure described in the pharmacy manual or the local site procedure.

Data Management and Statistical Evaluation is done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

This is an open label, uncontrolled, first-in-human trial of the BET inhibitor BI 894999 in patients with advanced solid tumours and in a cohort of patients with DLBCL, following a dose escalation trial design, based on BLRM with overdose control.

The starting treatment schedule was a continuous daily dosing in 3-week cycles. An additional intermittent dosing schedule with 2 weeks on and one week off treatment in 3-week cycles (Schedule B) was investigated in parallel, starting at the highest dose investigated in Schedule A in solid tumours which was considered to be safe by the DMC.

Once the MTD of both Schedules A and B in solid tumours was determined, the DLBCL cohort started using the MTD of the selected schedule (B) determined in the solid tumour cohort of this Schedule minus one dose level as the starting dose. This MTD determination in DLBCL was started in parallel with the MTD extension cohort in patients with solid tumours with the selected schedule (B). After MTD was confirmed for Schedule B in the patients with solid tumours, recruitment was opened to Phase Ib expansion cohorts in SCLC, mCRPC, CRC and NC patients with selected Schedule B. These cohorts are closed to recruitment at the time of protocol version 12.0 and only the cohort of NC patients with Schedule C is ongoing in the Phase Ib expansion.
The MTD will also be determined with Schedule C in DLBCL patients. Once the MTD of both Schedules B and C in DLBCL will be determined, the MTD cohort in DLBCL patients will be further extended using the selected schedule (B or C) to have a total of 12 to 14 DLBCL patients treated at the MTD of the selected schedule.
In parallel to MTD determination in DLBCL for both Schedules B and C, a Schedule C was tested in patients with solid tumours to determine the MTD in this schedule and then the MTD cohort will be further extended to up to 12 patients.

An escalation with overdose control design will increase the chance of treating patients at efficacious doses while reducing the risk of overdosing. This design is based on practical experience and is a preferable algorithmic method due to its superior ability to identify the dose with the desired toxicity rate and its allocation to a greater proportion of patients to doses at or close to that dose (R13-4802, R13-4804, R13-4805).

3.3 SELECTION OF TRIAL POPULATION

A log of all patients enrolled into the trial (i.e. who have signed informed consent) is maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

Patients with advanced, unresectable and/or metastatic solid tumours, who have failed conventional treatment or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies are eligible for the escalation part (Phase Ia) of this trial.

For patients in the DLBCL cohort, eligible patients are patients with histologically confirmed DLBCL, for whom there are limited or no standard treatment options available.

Fresh tumour biopsies at screening and under treatment, between Day 8 and Day 11 of the first cycle are mandatory for patients with solid tumours treated in the expansion Phase Ib with Schedule B. The fresh tumour biopsies at screening may be replaced by sending of archival tumour tissue provided that it was taken from the most recent relapse and not older than 6 months. The on treatment biopsy may remain optional if no easily accessible lesions are available.
Tumour biopsies are however not requested for mCRPC patients with only bone metastases and for patients with therapeutic INR because of treatment with a vitamin K antagonist or a novel oral anticoagulant. The tumour biopsies remain optional for NC patients and for patients with solid tumours or DLBCL treated in the Phase Ia, including the MTD extension cohorts. The platelet count and coagulation must be checked prior to each biopsy and must be adequate with platelets of at least 50 000/mm^3 without the support of transfusion and normal coagulation parameters. Should the biopsy under treatment with Schedule B, between Day 8 and Day 11 of Cycle 1 not be feasible in 5 of the first 20 patients of Phase Ib (see 3.1), the timing of biopsy under treatment in Cycle 1 will be moved ahead, between Day 3 and Day 8 for the next patients.
Patients in the expansion part (Phase Ib) must in addition to the Phase Ia criteria for solid tumours, have progressive disease within the last 6 months and have one of the four types of solid tumours selected for the expansion cohorts. The tumours that are investigated in the four expansion cohorts of Phase Ib are SCLC, mCRPC, CRC and NC out of which only the NC cohort with Schedule C is ongoing at the time of protocol version 12.0.

Patients who are responding to treatment or who are benefiting from treatment may provide optional consent to undergo a fresh tumour biopsy (platelet count and coagulation must be checked prior to the biopsy and must be adequate, see above) at the time of response and also provide optional consent for their archival tumour sample to be analysed. If they give consent for these to be done, a sample of 2-3 mL EDTA blood DNA tube is mandatory.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

3.3.2.1 In patients with solid tumours

1. Patients with a histologically or cytologically confirmed diagnosis of an advanced unresectable and/or metastatic, malignant solid tumour, who have failed conventional treatment or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies
2. Age ≥ legal age to be adult for the given country at the time of signature of the informed consent. For NC patients, age 15 years or older at the time of signature of the informed consent (in Germany and South Korea, only legally adult patients may be included)
3. Eastern Cooperative Oncology Group (ECOG, R01-0787) performance score 0 or 1 at the time of screening. A score of 2 is allowed for NUT carcinoma patients

4. Recovery of therapy-related toxicities from previous chemotherapy, tyrosine kinase inhibitors, hormone therapy, immunotherapy, antibodies, vaccine therapy, or radiotherapy to CTCAE ≤ grade 1 (with the exception of alopecia, peripheral sensory neuropathy grade 2)
5. Life expectancy of at least 12 weeks after the start of the treatment according to the investigator's judgement
6. Male or female patients. Women of childbearing potential* must be ready and able to use highly effective methods of birth control per ICH M3(R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information. For women of childbearing potential using a contraceptive pill, an additional barrier method is necessary due to the potential CYP3A4 inducing effect of BI894999. Male patients having a partner of childbearing potential must use condoms and ensure their partner is using a highly effective method of birth control as described above, during the trial and for at least three months after the end of the trial treatment

   * Any female who has experienced menarche and does not meet the criteria for "women not of childbearing potential" as described below.

   Women not of childbearing potential are defined as: women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).
7. Written informed consent consistent with ICH-GCP and local legislation. For adolescent NC patients aged 15 years to adult legal age written assent of the patient and written informed consent of the parents (both or one according to national regulation) or legal guardian of the adolescent
8. Written informed consent for tumour biopsies in the escalation phase Ia
   a. Optional for those patients until extension of the MTD cohort,
   b. Optional for the patients in the extension of MTD cohort at the same time points as described below for the expansion phase. For these patients in the extension of the MTD cohort, if they have an accessible lesion for biopsy, they will be offered optional consent for tumour biopsies

In addition, all patients included in the expansion Phase Ib must:

9. Have been diagnosed with one of the four types of tumours selected:
   a. small cell lung cancer (SCLC)
   b. metastatic castrate resistant prostate cancer (mCRPC)
   c. colorectal cancer (CRC)
   d. NUT carcinoma (NC) (for which the "midline" origin is not a prerequisite)
10. Have failed conventional treatments or who are not amenable to standard therapies (per criterion 1) that specifically include for:
    a. SCLC: a platinum-based therapy (previous treatment with topotecan is not mandatory)
    b. mCRPC: a hormonal agent (abiraterone, enzalutamide, or apalutamide) and a taxane (docetaxel or cabazitaxel)
    c. CRC: fluoropyrimidine, oxaliplatin and irinotecan, bevacizumab for patients eligible to this treatment and an anti-epidermal growth factor receptor (EGFR) in RAS (Rat Sarcoma Virus) wild type metastatic CRC.
11. Have measurable disease (radiated lesions and lesions used for biopsy do not qualify as target lesions), according to RECIST 1.1 (R09-0262) (for NC patients only non-

measurable disease is acceptable); or according to PCWG3 (R17-3377) for the mCRPC cohort (see point 5 of inclusion criteria below, specific to mCRPC patients)
12. Have progressive disease within the last 6 months, according to RECIST 1.1 (R09-0262) or according to PCWG3 (R17-3377) for the mCRPC cohort (see point 5 of inclusion criteria below, specific to mCRPC patients). NC patients do not need to show progression per RECIST 1.1 (for example, if newly diagnosed).
13. Have a tumour lesion accessible for biopsies (pre- and at steady state under treatment in Cycle 1, ideally from the same anatomic lesion) (except for mCRPC patients having only bone metastases or for patients with therapeutic INR because of treatment with a vitamin K antagonist or a novel oral anticoagulant. Biopsies are optional for NC patients
14. Give written informed consent for two tumour biopsies, one at screening and one after start of treatment, between Day 8 and Day 11 of Cycle 1 (or between day 3 and day 8 if the day of biopsy in Cycle 1 needs to be moved as explained in Section 3.1) (when applicable)

In addition, all patients in the mCRPC expansion cohort of Phase Ib must have:
15. Histologically or cytologically confirmed adenocarcinoma of the prostate
16. Radiographic evidence of metastatic prostate cancer (stage M1 or D2). Distant metastases evaluable by bone scan, CT scan, or MRI within 28 days before the start of study treatment.
17. PSA ≥ 5 ng/mL (if no measurable disease by RECIST 1.1)
18. Prior surgical or chemical castration with a serum testosterone of <50 ng/dL (< 1.7 nmol/L) by luteinizing hormone releasing level hormone (LHRH) agonist or antagonist, or by abiraterone or by enzalutamide or apalutamide. If the actual method of castration is LHRH agonist or antagonist, the patient must be willing to continue the use of LHRH agonist or antagonist during protocol treatment.
19. Progressive disease defined as at least one of the following:
    a. Progressive measurable disease: using conventional solid tumour criteria RECIST 1.1
    b. Bone scan progression: at least two new lesions on bone scan plus a rising PSA as described in point c below
    c. Increasing PSA level: at least two consecutive rising PSA values over a reference value (PSA no.1) taken at least 1 week apart. A third PSA (PSA no. 3) is required to be > than PSA no. 2; if not, a fourth PSA (PSA no. 4) is required to be > to PSA no. 2

3.3.2.2 In patients with DLBCL

1. Patients with histologically confirmed DLBCL who have failed 2 or more lines of systemic therapy including an anti-CD-20 therapy and an anthracycline or who are not amenable to standard therapies but have an indication for therapy as per investigator's judgement. Standard therapies may also include but are not limited to CAR-T cells therapy, depending on approved therapies in the country where the patient is treated
2. Age 18 years or older at the time of signature of the informed consent
3. ECOG Performance Status 0, 1 or 2 at the time of screening
4. Measurable disease (radiated lesions do not qualify as target lesions) according to RECIL 2017 (R17-3378) on the CT scan part of the FDG/PET-CT scan
5. Recovery of therapy-related toxicities from previous anti-lymphoma therapy to CTCAE ≤ grade 1 (with the exception of alopecia, peripheral sensory neuropathy grade 2)
6. Life expectancy of ≥12 weeks according to the investigator's judgement

7. Male or female patients. Women of childbearing potential* must be ready and able to use highly effective methods of birth control per ICH M3(R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information. For women of childbearing potential using a contraceptive pill, an additional barrier method is necessary due to the potential CYP3A4 inducing effect of BI894999. Male patients having a partner of childbearing potential must use condoms and ensure their partner is using a highly effective method of birth control as described above, during the trial and for at least three months after the end of the trial treatment
   * Any female who has experienced menarche and does not meet the criteria for "women not of childbearing potential" as described below.
   Women not of childbearing potential are defined as: women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).
8. Written informed consent which is consistent with ICH-GCP guidelines and local Legislation
9. Written informed consent for tumour biopsies (optional)

3.3.3 Exclusion criteria

3.3.3.1 In patients with solid tumours

1. Inability to swallow tablets
2. Additional other serious illness, concomitant non-oncological disease (e.g. active infectious disease including an active infection with SARS-CoV-2 confirmed by a PCR test or had one in the prior 6 weeks or active hepatitis (Hep) B infection as defined by positive Hep B DNA test, active Hep C infection as defined by positive Hep C RNA test and human immunodeficiency virus (HIV) infection (positive result in established HIV diagnostic assay), or ongoing toxicity from prior therapies considered by the investigator to potentially compromise patient's safety in this trial
3. History or presence of cardiovascular abnormalities deemed clinically relevant by the investigator such as uncontrolled hypertension, congestive heart failure NYHA classification of 3, unstable angina or poorly controlled arrhythmia. Myocardial infarction within 6 months prior to study entry. LVEF less than 50% at baseline
4. Clinical evidence of symptomatic progressive brain or leptomeningeal disease during the last 28 days before the start of treatment with BI 894999
5. Second malignancy currently requiring another anti-cancer therapy
6. Absolute neutrophil count less than 1500/mm^3
7. Platelet count less than 100 000/mm^3
8. Bilirubin greater than 1.5 mg/dL (>26 µmol/L, SI unit equivalent) (except known Gilbert's syndrome (accepted up to 2 mg/dL or up to 34.2 µmol/L in this case)
9. Aspartate amino transferase (AST) and/or alanine amino transferase (ALT) greater than 2.5 times the upper limit of normal (in the presence of liver metastases, greater than five times the upper limit of normal)
10. Serum creatinine greater than 1.5 mg/dL (>132 µmol/L, SI unit equivalent)
11. Women who are breastfeeding, pregnant or who plan to become pregnant while in the trial
12. Previous treatment with a BET inhibitor. Previous treatment with a BET inhibitor is however allowed for NC patients

13. Treatment with other investigational drugs or participation in another clinical interventional trial within the past four weeks (past two weeks for NC patients) or within five times the half-life of the previous investigational drug, whichever is the shorter, before start of therapy or concomitant with this trial
14. Systemic anti-cancer therapy within four weeks (past two weeks for NC patients) or five times the half-life of the drug, whichever is shorter. Radiotherapy given for curative intent within the past four weeks before start of therapy or concomitantly with this trial. These restrictions do not apply to LHRH agonists or antagonists, steroids (given at a stable dose in the last four weeks) used for palliative intent, bisphosphonates, denosumab and to palliative radiotherapy (no wash out required)
15. Patients unable to comply with the protocol
16. Patients who are actively abusing alcohol or drugs. Since no alcohol or drug testing is required per protocol, it is at the investigator's discretion to determine abuse.

3.3.3.2 In patients with DLBCL

1. Patient is eligible for curative salvage high dose therapy followed by stem cell transplant.
2. Primary central nervous system (CNS) lymphoma or known CNS involvement
3. Prior allogeneic bone marrow or stem cell transplant
4. Second malignancy currently requiring another anti-cancer therapy
5. High-dose therapy with stem cell support <3 months prior to visit 1
6. Inability to swallow tablets
7. AST or ALT >2.5 x upper limit of normal (CTCAE grade 2 or higher)
8. Total bilirubin >1.5 x upper limit of normal (CTCAE grade 2 or higher)
9. Absolute neutrophil count <1.0 x 10^9/L (without growth factor support)
10. Platelets <100 x 10^9/L (without transfusions)
11. Serum creatinine > 1.5 mg/dL (>132 µmol/L)
12. Significant concurrent medical disease or condition which according to the investigator's judgement would either compromise patient safety or interfere with the evaluation of the safety of the test drug, *e.g.* LVEF less than 50% at baseline, symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction within 6 months prior to study entry, cardiac arrhythmia requiring therapy with the exception of extra systoles or minor conduction abnormalities
13. Chronic or ongoing infection requiring treatment at the time of enrolment or within the previous two weeks, e.g. active infectious disease including an active infection with SARS-CoV-2 confirmed by a PCR test or one in the previous 6 weeks or active Hep B infection as defined by positive Hep B DNA test, active Hep C infection as defined by positive Hep C RNA test and HIV infection (positive result in established HIV diagnostic assay)
14. Women who are breastfeeding, pregnant or who plan to become pregnant while in the trial
15. Patients who are actively abusing alcohol or drugs. Since no alcohol or drug testing is required per protocol, it is at the investigator's discretion to determine abuse.
16. Previous treatment with a BET inhibitor
17. Treatment with other investigational drugs or participation in another clinical interventional trial within the past two weeks or within five times the half-life of the previous investigational drug, whichever is the shorter, before start of therapy or concomitant with this trial

18. Systemic anti-DLBCL therapy within the past two weeks or five times the half-life of the drug, whichever is shorter (palliative radiotherapy and agents used for palliative reasons for example steroids and bisphosphonates, are allowed)
19. Patients unable to comply with the protocol

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

A patient has to be withdrawn from the treatment and/or the trial if:

- The patient withdraws consent for study treatment or study participation, without the need to justify the decision
- The patient is no longer able to participate (e.g. severe AEs, surgery, disease progression, concomitant diagnoses, concomitant therapies or administrative reasons, occurrence of a second cancer). The investigator may also stop the patient's participation, if the patient is no longer able to attend the visits e.g. due to worsening of disease. For NUT carcinoma, patients are allowed to continue the trial treatment after progression as long as, based on the investigator's judgement, they have a clinical benefit to continue and there are no further treatment options available
- If eligibility criteria are violated in such a way that it might put the patient at risk if they continue on the trial treatment or the patient fails to comply with the protocol (e.g. non-compliance to study visits, to study treatment)
- The patient experiences a COVID-19 infection confirmed by a PCR test and the Investigator judges that the benefit-risk balance is not in favour of resuming treatment with BI 894999 after recovery from the infection

For all patients the reason for withdrawal (e.g. AEs) must be recorded in the electronic Case Report Form (eCRF). These data will be included in the trial database and reported.

As soon as a patient is withdrawn from the trial and given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and in Section 6.2.3.

After withdrawal, the patient will further receive the available treatment for his condition at investigator's discretion.

Patients withdrawn for another reason than DLT or patients who miss more than one visit during their first treatment cycle will be replaced. Patients who miss one visit may be replaced after discussion between the sponsor and the investigator if the information that needed to be collected during this visit is not available and makes the patient non-evaluable for pharmacokinetics analyses or safety parameters (including evaluation for DLT).
Patients who take incomplete doses or miss two doses or more of BI 894999 during their first treatment cycle for other reasons than toxicity will be replaced.
Patients who come off study due to DLT will not be replaced.

If a patient should become pregnant during the trial, the treatment with BI 894999 must immediately be stopped. The patient will be followed up until delivery or termination of

pregnancy (see Section 5.3.7). The data of the patient will be collected and reported in the CTR until last patient last visit and any events occurring thereafter will be reported in BI drug safety database.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim, after consultation with DMC, reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial. In such case the patient will be withdrawn from treatment and discontinued from trial. Further treatment will be based on investigator's judgment
3. Violation of good clinical practice (GCP), the clinical trial protocol (CTP), or the contract disturbing the appropriate conduct of the trial

The Investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

4.1.1 Identity of BI investigational product(s)

Table 4.1.1: 1 Test product

[redacted]	[redacted]
[redacted]	[redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4.1.2 Method of assigning patients to treatment groups

The first part of the study is an open label, dose escalation Phase Ia study. Patients with solid tumours will enter treatment according to the next available slot determined via an Interactive Response Technology (IRT) system, at the time they are enrolled, being it for Schedule A, for Schedule B or for Schedule C. The DLBCL cohort of selected schedule (B) was only opened to DLBCL patients once the MTD had been determined for both Schedules A and B in patients with solid tumours and the recommended Schedule had been determined by the DMC (Schedule B). Starting from protocol version 11.0 onwards, DLBCL patients will enter Schedule C for MTD determination after MTD has been determined for Schedule B. After DLBCL Schedule C dose escalation is complete, the DMC will then recommend the Schedule to further use for the extension of the DLBCL MTD cohort.
For Schedule C dose finding in patients with solid tumours, only a limited number of sites in Belgium will recruit patients (e.g., the two initial sites in Belgium at the start of schedule C, with the possibility to extend to additional Belgian sites, as needed) and for these sites, Phase

Ia inclusion will have privilege over Phase Ib, should a patient be eligible for any of the two parts of the study.

In the second part (Phase Ib), patients were treated with the schedule and dose determined by the DMC based on the safety, pharmacokinetic and biomarker results from the Phase Ia part in solid tumours, which was Schedule B. Furthermore, only patients with one of the four types of solid tumours were enrolled to Part Ib. Once MTD was determined for Schedule C in solid tumours patients of Phase Ia, and the DMC recommended Schedule C as selected schedule for further recruitment of patients in the NC cohort, the NC cohort with Schedule B was closed and a NC cohort with Schedule C opened for up to a maximum of 40 patients.

At the end of the screening period or during the first visit of Cycle 1, once the patient's eligibility is confirmed but before any drug administration, the dose and the bottles of treatment are assigned via IRT. To facilitate the use of the IRT, the investigator receives all necessary instructions in the ISF.

4.1.3 Selection of doses in the trial

4.1.3.1 First cycle of administration of BI 894999

Table 4.1.3.1: 1 Treatment schedule

Treatment at start of the study:	Schedule A	The starting schedule was continuous daily intake in cycles of 21 days
Treatment alternative which started in parallel to Schedule A	Schedule B	continuous daily intake for 14 days followed by one week off treatment in cycles of 21 days
Treatment alternative which started in parallel to Schedule B in DLBCL and to Phase Ib	Schedule C	Once daily loading dose on Day 1 followed by six days daily intake of maintenance dose, followed by one week off, repeated every two weeks in cycles of 28 days

A starting dose of 0.2 mg once per day was determined to be the safe starting dose in humans (see Section 1.2.2) with Schedule A.

Initially, only 1 patient was entered into each cohort, until the observation of a **drug-related AE CTCAE ≥ grade 2** during Cycle 1 (21 days), for the AEs listed below only:

- Clinical: all AEs except alopecia, inadequately treated nausea, vomiting or diarrhoea, fatigue if there is only one CTCAE grade of difference between the baseline condition and the worsening of fatigue.
- Laboratory parameters:

- Haematology: neutropenia, leukopenia, thrombocytopenia
- Biochemistry: increased liver function tests (AST, ALT, bilirubin and alkaline phosphatase), increased creatinine.

Once a patient experienced such a drug related AE, the single patient cohort was expanded to a total of 3 patients. This cohort and all subsequent dose cohorts were then to be treated according to a BLRM.

For any dose-escalation cohort after a drug related CTCAE ≥ grade 2 (as listed above) during Cycle 1 was observed, at least 3 patients were required, but two out of those patients must be evaluable patients (DLT evaluation in 21 days of first cycle for Schedules A and B, in 28 days of first cycle for Schedule C) to make the decision on the dose for the next patients/cohort. The DMC will also recommend the size for the next cohort up to six patients. However, the final decision on the next cohort size will be made by a mutual decision between the TMM and the Coordinating Investigator.
After all patients in a cohort have either experienced a DLT or have been observed for 21 days in the first cycle without experiencing a DLT (28 days in the first cycle for Schedule C), the BLRM will be updated with the newly accumulated data and the overdose risk will be calculated. Based on the model and on additional information (e.g. patient profiles, PK, pharmacodynamics biomarkers) when available at the time of decision, the members of the DMC will reach a joint decision on the next dose level to be investigated.
For each new dose tier, the second patient may only be included from day 8 onwards in the first cycle of the first patient. If no serious drug-related AE (serious adverse event (SAE)) occurs in the first patient, the next patients within the same cohort may be simultaneously included. The decision regarding the magnitude of the dose escalation/de-escalation steps will only be taken by the DMC, considering toxicity data from each patient cohort.

During the expansion phase, a patient who experiences a DLT will undergo dose de-escalation in the same way as patients treated in the dose escalation phase but the occurrence of a DLT will not lead to a change in MTD. However any DLTs occurring in the expansion Phase Ib will be considered in the evaluation of the recommended Phase II dose and schedule. In the NC population of the expansion phase, the DMC will have meetings after the first and after the second adolescent patient finishes the first cycle to assess whether the adult dose is tolerable in adolescents.

4.1.3.2 Additional cycles of BI 894999

Patients who tolerate the trial drug and experience at least disease stabilisation or an improvement of disease-related symptoms according to the investigator's judgement may continue treatment. The dose of BI 894999 administered in further cycles must be the same as the dose administered in the previous cycle, unless the patient experienced dose limiting toxicity or any drug related significant AE necessitating a dose reduction according to investigator's judgement (see Section 4.1.4).

4.1.4 Drug assignment and administration of doses for each patient

At the first visit of each cycle, the patient will receive the necessary amount of medication bottles from the applicable strength(s) to cover for the cycle period. The treatment numbers of the bottles will be assigned via the IRT system (see Section 4.1.2). If slots were available to patients with solid tumours at the same time in Schedules A and B, patients were allocated in priority to Schedule A in order to determine MTD. If slots were available at the same time in Schedule C and in the expansion Phase Ib in one of the sites participating in recruitment for Schedule C in patients with solid tumours, patients were allocated in priority to Schedule C in order to determine MTD. For DLBCL slots, patients are included in Schedule C since MTD has been determined for Schedule B.
The trial drug administration will happen at the clinical site on the days of visits or outside the clinical site on the other days, in the morning of each day, at approximately the same hour of the day if possible (e.g. 1h before breakfast, except for the [redacted] cohort), according to the schedule (see Flow Chart).
Patients experiencing emesis may not take a replacement dose.
If a patient forgets to take a dose, he/she may not take it if more than 3 hours elapsed after the normal hour for intake. He/she will then simply take the next dose at the planned time. The patient will be instructed to never take two doses to make up for the forgotten dose as BI 894999 must not be taken more than once a day under any circumstances.
During the COVID-19 pandemic, physical visits to the sites may need to be restricted to ensure patient's safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue the trial treatment and trial medication may be shipped to the patient's home if acceptable according to local law and regulations. This will also be applicable in the post-pandemic context, after approval of protocol version 12.0 (for more details see Sections 6.1 and 10.5).

4.1.4.1 Cycle 1

The trial drug administration should be started in the morning of the first treatment day. The assigned dose for a patient, according to the dose tier and treatment schedule will be administered at the investigational site on the morning of Day 1, after an overnight fast and 1 hour before breakfast (with exclusion of the patients participating to the food interaction sub-study, see Section 10.2.2), and the tablets must be swallowed with at least 250 mL water. On Day 2, while the patient is still kept at the institution, the dose is given after the PK sample and whole blood sample for [redacted] gene expression at 24h post-dose have been taken (not applicable anymore for NC patients and DLBCL patients after protocol version 12.0 approval where the visit of Day 2 is cancelled).
The next doses will be taken by the patient outside of the clinical site up to day 7 (except third dose for the [redacted] cohort, see Appendix 10.2.2).
On the mornings of Day 8 and Day 12 for Schedules A and B, the patient came to the investigational site with his/her medication bottle(s) without having taken his/her morning dose and he/she received his/her dose after the necessary visit procedures happened, including PK sample before the drug was administered (see Appendix 10.2).
For Schedules A and B, on Day 14 and Day 15 (not on Day 15 in Schedule B), the dose was given at the investigational site after the PK sample and whole blood samples for HEXIM1 gene expression pre-dose and at 24h post-dose had been taken. In Schedule B, the medication

bottle(s) were returned to the site on Day 14. For Schedule C, on Day 15 and on Day 21, the dose is given at the investigational site, on Day 21 after the PK sample and whole blood samples for HEXIM1 gene expression pre-dose have been taken.
The other doses of the cycle will be taken by the patient outside of the clinical site.
On all days when there is no safety lab sampling to be taken which includes fasting blood glucose, the patient should however have an overnight fast before the drug intake and should not eat until one hour after drug intake. Medication should not be taken together with a meal.
On Day 22 in Schedule A, the patient returned the medication bottle(s) from Cycle 1 to the investigational site. For the three Schedules, he/she will receive his/her dose of the first day of next cycle, if applicable, from the bottle(s) of the second cycle, after the necessary visit procedures happened.
The exact time of trial medication intake on the investigational site must be recorded in the eCRF as this information is crucial for proper evaluation of pharmacokinetics and other data.
Tumour biopsy (where applicable) must be performed in Cycle 1, between Days 8 and 11 (between Day 3 and Day 8 if not feasible between Day 8 and Day 11 (see 3.1) for patients in Schedule A or B, between Days 18 and 21 for patients in Schedule C), 4h to 8 h after the daily dose of BI 894999 has been taken.

The patient will record the date and time of each medication intake during the first cycle in a diary to help with the compliance check.
Each time the patient comes to the trial site for a visit (up to Day 14 in Schedule B, up to Day 21 in Schedule C) he/she will bring his/her medication bottles and patient diary card (in first cycle) and a compliance check must be performed. Discrepancies between the number of tablets remaining and the number of tablets the patient should have taken must be documented and explained, whenever possible (see 4.3).

During the first cycle, the patient may interrupt treatment (not including the one week scheduled treatment break in Schedule B or the two times one week treatment break in Schedule C) only in case of a DLT (see 5.3.6.1) or at the end of the evaluation period of 21 days (28 days in Schedule C) for recovery of another drug-related AE of CTCAE grade 3 or 4.

4.1.4.2 Further Cycles

For all subsequent cycles, the medication intake will happen outside of the clinical site except on the first day of each cycle (first two days for Cycle 2 in Schedule B, Days 1 and 15 in Schedule C) when it has to be administered at the trial site following an assessment by the investigational team, and he/she will have to return all the received medication bottles at the end of cycle visit.
Starting from protocol version 12.0 onwards, for NC and DLBCL patients, if the patient is unable to travel frequently to the site and if deemed safe by the investigator, the investigator may instead organize for the patient to have examinations of visit on Day 15 of any Cycle after Cycle 1 performed locally, close to the patient's home, if allowed by local country regulations. The investigator must ensure that the persons and facilities executing the local tests are adequately qualified for performing those tests. The investigator will then have, as a minimum, a phone call visit with the patient to evaluate the patient's safety based on [redacted] conversation with the patient and the results from the local tests. In this case, the patient will take his medication at home on Day 15 of the cycle.

The Day 1 tests of even cycles, from Cycle 6 onwards may also be performed locally, close to the patient's home with a phone call visit with the site investigator to evaluate the patient's safety, if the patient is unable to travel frequently to the site. It means that a drug dispensation may happen for two consecutive cycles on Day 1 of uneven cycles starting from C5 onwards, after discussion with the Sponsor, and if deemed safe by the Investigator. Alternatively, if applicable by the local regulation in the given country, a direct shipment from the site to the patient may happen, but in this case, via a courier approved by the Sponsor and aware of the procedure set-up by the Sponsor to ensure the correct conditions of the shipment.

In parallel to Schedule A an alternative Schedule B was started at the same dose tier at which the highest safe continuous daily dosing in 3-week cycles was investigated, according to DMC decision. An additional Schedule C was tested in patients with solid tumours, in parallel to Schedule B dose finding in DLBCL patients, starting with the recommended phase Ib dose of 2.5 mg as maintenance dose from Day 2 to Day 7 and from Day 16 to Day 21 and a loading dose of 5 mg on Day 1 and Day 15, in 4-week cycles.
As the MTD was determined for DLBCL patients in Schedule B, the Schedule C is also being tested in patients with DLBCL, starting with a loading dose of 4 mg and a maintenance dose of 2 mg in the first cohort.
For a patient to be eligible for treatment with further cycles, the following criteria must be met:

- Absence of disease progression (except for NC patients deriving clinical benefit and for whom no other treatment option is available)
- Acceptable tolerability: patients experiencing DLT are eligible for further treatment cycles with BI 894999 at one dose tier below as soon as recovery from drug related toxicities allows further treatment. This means for Schedule C, a reduction of the loading dose in steps of 1 mg and a reduction of the maintenance dose in steps of 0.5 mg (e. g., for the first cohort, the loading dose would be reduced from 5 mg to 4 mg, from 4 mg to 3 mg, from 3 mg to 2 mg while the maintenance dose would be decreased from 2.5 mg to 2 mg, from 2 mg to 1.5 mg, from 1.5 mg to 1 mg).

Patients eligible for a further (repeat) treatment cycle will not start before day 22 after start of the previous cycle (Day 29 for Schedule C).
Before the start of each next cycle, any remaining medication from the previous cycle must be collected. If the patient is eligible for a further cycle of treatment, new bottle(s) must be dispensed.

4.1.4.3 Dose interruptions and reductions

4.1.4.3.1 Dose interruptions

Dosing will be interrupted for any patient that experiences a dose limiting toxicity as defined in 5.3.6.1.
Patients may continue therapy at a reduced dose of BI 894999 only after recovery from the DLT to at least CTCAE grade 1 or baseline level (except peripheral sensory neuropathy, anaemia or lymphopenia where treatment continuation is allowed at CTCAE grade 2).
At the end of the 21 day cycle, for Schedules A and B or 28 day cycle for Schedule C, dosing may be interrupted (i.e. start of next cycle postponed) at investigators discretion for recovery of other drug-related AEs of CTCAE grade 3 or 4 that do not qualify for DLT.

AEs of increased troponin
A CTCAE grade 3 troponin increase that is considered to be drug related qualifies for DLT according to 5.3.6.1 and will lead to an immediate dose interruption and additional cardiac investigations (e.g., review by a cardiologist, CK/CKMB, ECG, echocardiography) must be performed as soon as possible to determine whether there is evidence of relevant cardiotoxicity. Only in case these investigations rule out new or emerging cardiotoxicity, the patient can resume treatment with BI 894999 upon recovery of the troponin increase to a grade 1 or baseline and at a reduced dose according to the DLT rules (see 4.1.4.3.2). Intensified cardiac monitoring will be performed in these cases by evaluation of LVEF before the re-start of treatment and every 2 cycles thereafter to detect any new impaired wall motility or an indisputable drop of LVEF (percentage points reduction of ≥10 from baseline value or drop of LVEF below 50%, corresponding to a CTCAE grade 2) which would lead to drug discontinuation.

AE of COVID-19 infection
In case of COVID-19 infection confirmed by a PCR test, the treatment with BI 894999 should be interrupted until recovery. The patient may resume treatment following recovery if the patient is expected to derive clinical benefit, as agreed between the Investigator and the Sponsor.

4.1.4.3.2 Dose reductions

If an AE is a DLT, the dose of BI 894999 must be reduced and treatment can continue only after sufficient recovery as explained in Section 4.1.4.3.1.
In case of DLT, the new dose of BI 894999 will be the one used at the previous dose tier of one of the treatment schedules used in the study (e.g., dose reductions from 2.5 mg to 2 mg, from 2 mg to 1.5 mg, from 1.5 mg to 1 mg). For Schedule C this applies to the loading dose which will be decreased in steps of 1 mg while the maintenance dose will be decreased in steps of 0.5 mg.
If an AE is not a DLT, the dose of BI 894999 should be kept the same and treatment can continue only after sufficient recovery as explained in Section 4.1.4.3.1. The BI 894999 dose may be reduced as a result of non-DLT AEs if deemed safer for the patient by the investigator.

For patients delaying the subsequent cycle by more than 14 days because of a drug related AE, treatment should be continued at a reduced dose.

Once a dose reduction occurred, the patient must continue at the reduced dose and cannot be re-escalated later on.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Not applicable in this open-label trial.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

For details of packaging and the description of the label, refer to the ISF.
BI 894999 will be supplied as film coated tablets. [redacted]

Bottles are labelled according to local regulations and include the following as a minimum;

- Study number (1367.1)
- Product name (BI 894999)
- Contents of the bottle (30 tablets/bottle)
- Tablet strength
- Batch number
- Medication number
- Use-by date
- Storage information
- Instructions for use
- Sponsor name and address
- A statement that the medication is for clinical trial use
- A caution statement that the medication has to be kept out of the reach and the view of children.

The necessary bottles of medication are to be dispensed on day 1 of each cycle, regardless of the number of tablets remaining in the bottle(s) from the previous cycle which is collected on day 1 of each next cycle. In the event that dose reduction is necessary, the patient will return to the clinic and new medication will be dispensed, at the new dose level.

4.1.7 Storage conditions

Drug supplies are to be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately."

4.1.8 Drug accountability

The pharmacist (or the investigator where legally authorized) will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by an Institutional Review Board (IRB) / an independent ethics committee (IEC),
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,

- Availability of the curriculum vitae of the principal Investigator,
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the Principal Investigator where applicable
- Availability of FDA Form 1572 (for US sites)

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.

The pharmacist (or the investigator where legally authorized) must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the Sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre wil1 maintain records of the disposal.

These records must include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The pharmacist (or the investigator where legally authorized) must maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the Sponsor. At the time of return to the Sponsor or appointed CRO or alternative disposition, the pharmacist (or the investigator where legally authorized) must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

Rescue medication to reverse the action of BI 894999 is not available.

Potential adverse reactions of BI 894999 have to be treated symptomatically.

In patients with DLBCL who are at risk of developing Tumour Lysis Syndrome (TLS), it is up to the investigator's discretion what monitoring and precautionary measures are to be taken (for example, hydration, administration of allopurinol or rasburicase) in these patients. In the event that a patient develops TLS, he/she should be treated according to the institutional or standard guidelines and the TLS reported as an AE.
Concomitant therapy must be recorded in the eCRF, during the screening and treatment period, starting at the date of signature of informed consent, and ending at the end of the residual effect period (REP), 30 days after the last study drug intake (see Section 5.3.7). For parenteral nutrition during the trial, the components need not to be specified in detail. It should just be indicated as 'parenteral nutrition'.
After the REP, only concomitant therapy indicated for treatment of a related AE has to be reported. The start of a new anti-cancer treatment will be documented in the eCRF on the patient's status page of the follow-up visit.

During the first cycle, the use of growth factors for treatment of evident haemato-toxicity is not allowed except under life-threatening circumstances in patients with solid tumours (allowed for DLBCL patients). After the first cycle, the use of haematologic growth factors (e.g. granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), erythropoietin, platelet-stimulating agents, pegylated G-CSF) in case of haematological toxicity of the experimental compound BI 894999 will be considered and discussed within the team if required. If this is the case, it has to be recorded in the eCRF including duration and dose of the treatment.

If any diarrhoea is experienced (CTCAE grade ≥2), the patient must be treated with antidiarrheal treatment according to the local standard (for example loperamide two 2 mg tablets taken immediately, followed by one 2 mg tablet with every loose bowel movement, up to a maximum daily dose of 8 tablets (16 mg)).
In the event of diarrhoea, patients must be advised to avoid lactose-containing products or any foods known to aggravate diarrhoea.
Oral hydration is essential regardless of severity; appropriate rehydration (1.5 L/m2/day plus equivalent of actual fluid loss) and electrolyte replacement has to be ensured in the event of CTCAE grade 2 and grade 3 AEs.
In case of nausea and/or vomiting, the patient must be treated according to the local standard or according to the recommendations given in the Consensus Statement of the Anti-emetic Subcommittee of the Multinational Association of Supportive Care in cancer (MASCC): Prevention of chemotherapy- and radiotherapy-induced emesis: results of the Perugia Consensus Conference (R06-0986).
Symptomatic drug treatments of adverse reactions or tumour-associated symptoms are allowed, including the use of LHRH agonists or antagonists, steroids (given at the lowest possible dose and for the shortest possible duration to keep interference with response evaluation at the minimum, if introduced during the study treatment period), bisphosphonates and denosumab.
It is possible that some patients treated with BI 894999 will experience concurrent severe thrombocytopenia and changes in coagulation lab assays. The coexistence of thrombocytopenia and changed coagulation lab results potentially increases the risk of bleeding events. In order to reduce the risk of bleeding events in patients with severe thrombocytopenia and prolonged coagulation times, mandatory prophylactic platelet transfusions need to be administered to all patients who present with a platelet count below 20 000/mm^3.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Additional systemic anti-cancer therapies or curative radiotherapy is not allowed during the study.
For symptom control, palliative radiotherapy is permitted for any lesion in the dose escalation part of the study, except during the first cycle if it is considered by the investigator and the TMM that it could interfere with the DLT evaluation for MTD determination. In the expansion phase (Part Ib), palliative radiotherapy is only allowed to non-target lesions, following discussion with the TCM, provided that the reason for radiotherapy does not reflect PD and does not interfere with response assessment (for NUT carcinoma patients, palliative radiotherapy to target lesions or to lesions that indicate PD is allowed for patients that are

deriving clinical benefit from the study treatment as confirmed by the investigator). Lesions that have been exposed to radiotherapy are no longer evaluable, and may not be included in the assessment of the non-target lesions (or target lesions for NC patients) and the overall assessment. These lesions may also not be used anymore for the study biopsy. Unless in emergency situations, the TCM should be contacted prior to the administration of palliative radiotherapy in the expansion phase.

During the first cycle, the use of growth factors for prevention or treatment of evident haemato-toxicity is not allowed in patients with solid tumours (allowed for DLBCL patients) except under life-threatening circumstances (see Section 4.2.1).

Because of the non-clinical (in vitro) finding of the potential CYP inducing effect of BI 894999 on CYP3A4, CYP 2C8 and CYP 1A2 , there is a risk that BI 894999 might reduce the plasma concentrations of some concurrent medications which are substrates of CYP3A4, CYP2C8 and CYP1A2, for example oral contraceptive pills, potentially resulting in a reduction in their effectiveness. There, the investigators should be aware of this when concomitant medications which are substrates of these CYP enzymes are given to the patient, with attention to a potential decrease of efficacy of the concomitant medication (a list of medications considered clinically relevant substrates of CYP 1A2, CYP 2C8 and CYP 3A4 is given in in Appendix 10.6).

4.2.2.2 Restrictions on diet and life style

The usual restrictions on diet and life style which were already applicable for a given patient before entry into the study, according to his/her medical condition, have to be continued.

During treatment with BI 894999, all study patients will be advised to avoid sun exposure or artificial UVA/UVB radiation in solaria or tanning booths. If exposure to sunlight cannot be avoided, protective clothing and broad spectrum (UVA/UVB) sunscreens must be used. After discontinuation of BI 894999 treatment, all protective measures must be continued for at least 1 week.

4.2.2.3 Restrictions regarding women of childbearing potential

Women of childbearing potential must be ready and able to use highly effective methods of birth control per ICH M3(R2) that result in a low failure rate of less than 1% per year when used consistently and correctly, and this during the trial and for at least six months after the end of the trial treatment (see Section 3.3.2 and explanation given in the informed consent information form for more information on highly effective methods of birth control). Women of childbearing potential taking a contraceptive pill as birth control method must use an additional barrier method for the entire duration of the study treatment intake and for up to one month after the end of the study treatment intake.
Male patients with partners of childbearing potential need to use condoms and ensure their partner is using an additional highly effective method of birth control, during the trial and until at least three months after the end of the trial treatment.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits. Based on tablet counts, treatment compliance will be calculated as the number of tablets taken, divided by the number of doses which should have been taken according to the scheduled period, multiplied by 100. Compliance will be verified by the on-site monitor authorised by the Sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablets from each strength actually taken} \times 100}{\text{Number of tablets from each strength which should have been taken}}$$

If the number of tablets taken is not between 80-100%, site staff will explain to the patient the importance of treatment compliance.

5. VARIABLES AND THEIR ASSESSMENT

Safety data will be collected and evaluated routinely on an ongoing basis.

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint(s)

5.1.1.1 Phase Ia

The primary endpoint for the Phase Ia part of the study is the number of patients with DLT (see Section 5.3.6.1 for definition of DLT) observed during the first treatment cycle (the first 21 days for Schedules A and B, the first 28 days for Schedule C), which will be assessed for dose escalation in order to meet the objective of the determination of the MTD of BI 894999 for each schedule in patients with solid tumours and for the Schedules B and C in the DLBCL cohort.

5.1.1.2 Phase Ib

For the Phase Ib part of this study, the primary endpoint is the number of patients with DLTs observed during the entire treatment period (as assessed approximately every 3 weeks, at the end of each new cycle after Cycle 2, every 4 weeks for Schedule C in the NC cohort if this cohort is opened to recruitment) for patients who are enrolled in one of the four pre-selected types of cancer in the Phase Ib part and are treated at the Phase Ib dose and schedule recommended by the DMC as determined from the Phase Ia part and ongoing safety data collected during Phase Ib.

All DLTs occurring during the entire treatment period will be considered for the evaluation of the recommended Phase II dose and schedule of BI 894999 and the recommended dose and schedule will be re-evaluated based on BLRM and other data collected from Phase Ib.

5.1.2 Secondary Endpoint(s)

Secondary endpoints are:

For Phase Ia

- the number of patients with DLTs (see Section 5.3.6.1 for definition of DLT) observed during all treatment cycles for each of the schedules (A, B and C) in patients with solid tumours and for the Schedules B and C in the DLBCL cohort

All DLTs occurring during the entire treatment period for Schedules A and B will be considered for the evaluation of the recommended Phase Ib dose of BI 894999.

All DLTs occurring during the first or repeated treatment cycles will be reported as significant AEs, as if an SAE (see Section 5.3.6.1).

For both Phases Ia and Ib:

- PK parameters after single dose and at steady state (C_{max}, AUC_{0-24}, $C_{max,ss}$ and $AUC_{\tau,ss,}$), measured during the first cycle (the first 3 weeks for Schedules A and B, the first 4 weeks for Schedule C)
- Objective response (OR), defined as CR or PR with tumour assessment during treatment period for each schedule (see 5.2.1). For DLBCL patients, a minor response according to RECIL 2017 is not part of an objective response

For Phase Ib:

- Progression-free survival (PFS) defined from date of start of BI 894999 to the date of objective disease progression or death, whichever is earlier, with tumour assessment every 2 cycles (every 6 weeks for Schedule B if no delays or as close as possible to the end of the second of the two cycles of treatment if there was a delay) during treatment period
  Or
  Radiological PFS with tumour assessment by bone scan every four cycles for mCRPC patients with non-measurable disease by RECIST 1.1
- Best overall response, with tumour assessment according to Section 5.2.1, depending on the type of solid tumour, during treatment period
- PSA response in patients with mCRPC (see 5.2.1)
- Overall survival in patients with NC. This will be for patients in the trial after approval of protocol version 11.0 and who gave consent to this collection. The overall survival status will continue until 12 months after the end of trial as defined in Section 8.6.

[redacted]

5.2 ASSESSMENT OF EFFICACY

5.2.1 Tumour assessment

The tumour response will be evaluated:

- using the RECIST 1.1 (R09-0262), with tumour assessment every 2 cycles (every 6 weeks if no delays for Schedules A and B, every 8 weeks for Schedule C or as close as possible to the end of the second of the two cycles of treatment if there was a delay) during treatment period for each schedule in all patients with solid tumours
- using PCWG3 (R17-3377) recommendation every 4 cycles (12 weeks if no delays or as close as possible to the end of the second of the four cycles of treatment if there was a delay) based on bone scan coupled with PSA percentage change at the same time-points as bone scan for mCRPC patients without measurable disease according to RECIST 1.1 in Phase Ib
- using RECIL 2017 (R17-3378) (see Appendix 10.7) based on FDG-PET/CT scans for selected schedule (A or B) in the DLBCL cohort every 2 cycles during first four cycles, then every four cycles. The assessment of overall response rate in DLBCL will only include patients who achieve a partial or a complete response

The assessment by the investigator and/or the local radiologist will be the basis for continuation or discontinuation of the trial in an individual patient (in addition to safety).
The baseline scan(s) (CTscan, bone scan, FDG-PET/CT scans, and/or MRI according to investigator's decision) from screening must have been performed within six weeks prior to treatment with the trial drug and the investigator will record results of assessment in the patient's medical records and in the eCRF before the start of treatment according to the assessment method:

- According to RECIST 1.1, the target (five target lesions in total and maximum two per organ) and non-target lesions at baseline.
- According to RECIL 2017, target (up to three target lesions in total) and non-target lesions at baseline.

- According to PCWG3: on bone scan, 2 new lesions are considered as progressive disease.

The same method of assessment and the same technique must be used to characterise each reported lesion at baseline and during treatment. Lesions in previously irradiated areas may not be considered measurable or evaluable at baseline unless the lesions occurred after irradiation. A tumour lesion used for biopsy is not to be considered as a target lesion.
Tumour response assessment will be performed every two cycles (every 4 cycles after Cycle 4 in DLBCL patients, every 4 cycles for bone scan in mCRPC patients) and at the EOT visit (if not performed within the last 6 weeks).

PSA evaluation in mCRPC patients:

- A PSA response is defined as a decline in PSA value ≥50% from baseline (which is confirmed by a second value 3 to 4 weeks apart)
- A PSA progression is a 25% or greater increase in PSA, and an absolute increase of 2 ng/mL or more from the nadir and which is confirmed by a second value 3 or more weeks later

A rising PSA corresponding to the definition of disease progression (see definition above) is not a reason on its own to stop with the trial treatment in mCRPC patients otherwise benefitting from the treatment but is considered as PD if concomitant with 2 new bone lesions on bone scan or PD according to RECIST 1.1 or clinical evidence of PD.

If the patient stops with the trial medication intake for another reason than PD, the tumour assessment according to RECIST, RECIL or PCWG3 will be performed according to standard of care until the last follow-up needed according to protocol (progression, death, lost to follow-up, end of the trial).

For the NC patients, the overall clinical benefit assessment per Investigator's judgement will be based on the following points:

- response (CR, PR or SD, mixed response)
- symptom relief such as pain, breathing problems, other improvements (Investigator to specify)
- other reason for considering the clinical benefit (Investigator to specify)

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

5.3.1.1 Physical examination, height, body weight, performance status

Physical examination will be performed at screening, on visit 1 of each cycle prior to study medication intake and at the EOT visit.

Physical examination will include e.g. measurement of height and of body weight and the evaluation of the ECOG performance score. Height will be documented only once during screening. Weight will be measured during screening, on visit 1 day 1 of each cycle, at the

EOT visit and at FU. The ECOG score will be assessed during screening, on visit 1 day 1 of each cycle, and at the EOT and FU visits.

For DLBCL patients, a tumour size determination (by palpation) will be performed at screening and at the first visit day of each cycle. For the lymph nodes, only the largest lymph node per area will be assessed in two dimensions (if greater than 1 cm in any diameter, which can be physically assessed). The spleen and liver enlargement will be expressed in cm below the costal margin. Any other tumour manifestation will also be evaluated in two dimensions.

5.3.2 Vital Signs

Vital signs (blood pressure, body temperature and pulse rate after 2 minutes supine rest) will be recorded at the screening visit, at every visit of the treatment cycles and at the EOT visit. In addition, during the first cycle, vital signs will be measured more frequently on PK sampling days (see Flow Chart).

5.3.3 Safety laboratory parameters

Blood (venous) samples will be collected at the times indicated in the Flow Chart and analysed by the site's local safety laboratory.
Laboratory tests will include the following safety lab parameters:

- Haematology

Red blood cell count (RBC), haemoglobin, haematocrit, mean corpuscular volume (MCV), white blood cell count (WBC) and differential expressed in absolute values, platelets

- Biochemistry

Fasting glucose (after overnight fast), sodium, potassium, calcium, phosphate, urea, creatinine, AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin, total protein, albumin, uric acid, creatine phosphokinase (CK) and highly sensitive (hs) troponin (T or I, according to the laboratory assay used at a given site, but always with the same method for a given patient) must be performed and the findings documented.

In case of significant troponin hs increase, further investigations according to standard clinical practice should be undertaken by the investigator as deemed appropriate (see Section 4.1.4.3.1).

Monitoring for TLS includes the following tests:
- uric acid, creatinine
- sodium, potassium, calcium, phosphate
- lactate dehydrogenase (LDH)

- Coagulation parameters

Prothrombin time (PT) (expressed in seconds and in international normalized ratio (INR)) and activated partial thromboplastin time (aPTT); at screening, in Cycle 1: on day 1 before the first

dose of BI 894999, on day 2, on day 8, on pre-dose on the day of tumour biopsy when applicable and on day 14, on the first day of every next cycle and on day 15 of Cycles 2, 3 and 4 and at EOT. In addition, activity of factors II, V, VII and IX will be measured in the first 20 patients of the Phase Ib in Cycle 1 on Day 1 before first dose of BI 894999 and on Day 14 as well as on Cycle 2 Day 1 pre-dose.
In patients with out of range coagulation lab results (PT, aPTT) in the routine safety laboratory assessments, additional coagulation investigations should be performed as appropriate and guided by the specific lab findings (such as analysis of single coagulation factor activity and mixing studies to distinguish factor deficiencies from inhibitors) in order to investigate the underlying reasons for the prolongation of coagulation times.

- Virology, only at screening (starting from protocol version 9.0 onwards)
  - Hep B DNA test,
  - Hep C RNA test
  - HIV test with an established HIV diagnostic assay

Tests results obtained within 4 weeks of screening are acceptable and must be negative for inclusion of the patient in the trial.

- Urine

Urine (pH, glucose, erythrocytes, leukocytes, protein, nitrite) will be analysed by dipstick (semi-quantitative measurements) during the screening visit, at visit 1 Days 1 and 2, at visits 4 and 5 of initial treatment cycle, at visit 1 of repeated treatment cycles and at the EOT visit. In case of pathological findings, further evaluation must be performed and the findings documented.

- Pregnancy test

Beta human chorionic gonadotrophin (β-HCG) pregnancy test in urine or serum will be performed for women of childbearing potential at screening, within 7 days prior to first study treatment and before the start of each repeated cycle as well as at the EOT visit.

These parameters will be assessed as specified in the Flow Chart. In case of toxicity, adequate and more frequent blood sampling is at the discretion of the investigator. In the event of grade 4 neutropenia or grade 4 thrombocytopenia, blood will be examined at least twice weekly after the first occurrence of the grade 4 until return to a lower grade and then further followed at the discretion of the investigator.
In case where laboratory investigations have been performed more than 72h prior to the first study treatment intake, the results of new laboratory investigations performed within 72h before the first treatment administration must be available and confirm eligibility.

5.3.4 Electrocardiogram

In Cycle 1, standard 12-lead resting (after at least 5 minutes rest in the supine position) ECGs matched with PK samples will be performed according to the Flow Chart and in the Appendix 10.2, as much as possible in triplicate. At screening and in patients eligible for repeated cycles of treatment, standard (triplicate) 12-lead resting digitalized ECGs must be done according to

the Flow Chart (before the intake of BI 894999 at the start of a new cycle) and whenever the investigator deems it necessary. An ECG will also be performed at the EOT visit and at the follow-up visit (optional if performed at the EOT visit and no drug related abnormalities were detected in on-study ECGs).

In case of drug related ECG changes, additional ECG monitoring will be performed in the respective and later cycles of treatment, as deemed necessary by the investigator.

All ECGs have to be digitally recorded, if possible in triplicates, within a period of maximum 3 minutes, using dedicated equipment provided by the CRO and sent electronically to the CRO.

When the ECG time point is concomitant with a blood sampling (or any other procedure), the ECG must always be performed prior to the blood sampling (or other procedure) to allow the recording in reproducible resting conditions. Detailed instructions for correct ECG recording are provided in the ISF.
If for a visit, the patient has the assessments performed locally and not on the clinical site, the ECG will not be performed on the central reading ECG device and the ECG tracing must be sent to the site which will send it to the Central Reading laboratory for evaluation.

The recordings will be checked for pathological results (to be recorded as AEs) by the investigator. In addition a centralised evaluation of all 12-lead ECGs will be performed by the CRO for all ECGs sent to them. This analysis will include the determination of RR-intervals, PR-intervals, QRS-intervals, QT-intervals. The CRO is also in charge of a safety over read of ECGs (one ECG out of every series of three) which will be done by a board-certified cardiologist. In case of clinical abnormalities detected by the cardiologist, the report will be provided to the investigator via email or fax by the central reading laboratory and will be reported as an AE by the investigator if not already spontaneously reported.
To allow for a heart rate correction of QT intervals the QT intervals will be matched to the preceding RR intervals using at least QTcF (Fridericia's formula $QTcF = QT * RR^{-1/3}$) and QTcB (Bazett's formula $QTcB = QT * RR^{-1/2}$).
When preliminary PK results are available (e.g. at the end of the escalation phase), ECG recording time points may be adjusted, or new time points may be added according to the pharmacokinetic profile of BI 894999.

5.3.5 Other safety parameters

5.3.5.1 Left ventricular ejection fraction

Due to the cardiac findings seen in some patients in this first in human trial as described in Section 2.3, the decision has been taken to add an echocardiography or MUGA scan at screening and then at the end of Cycle 2 and at EOT (if not performed within the last 6 weeks before and if the patient's health status allows), in order to assess the LVEF. Additional measures must be performed in case a grade 3 troponin increase is seen (see Section 4.1.4.3.1).
The same method of measurement (echocardiography or MUGA scan) should be used throughout the study.

Echocardiography should be performed according to the standard guidelines of the American Society of Echocardiography (ASE) (R16-5269).

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Serious adverse event
A SAE is defined as any AE which:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

Every new occurrence of cancer of new histology must be reported as a serious event regardless of the duration between discontinuation of the study drug and the occurrence of the cancer.

AEs considered "Always Serious"
In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above.
The latest list of "Always Serious AEs" can be found in the remote data capture (RDC)/electronic data capture (EDC) system. These events must always be reported as SAEs as described in section 5.3.6.1.

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.3.7.

The following are considered as AESIs:
Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

For patients with normal hepatic function at baseline
- an elevation of AST and/or ALT ≥3 fold the Upper Limit of Normal (ULN) combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, and/or
- marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

For patients with abnormal hepatic function at baseline (e.g., due to primary liver cancer or hepatic metastases)
- an elevation of AST and/or ALT ≥5 fold ULN combined with an elevation of bilirubin ≥2 fold ULN measured in the same blood draw sample.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "Drug Induced Liver Injury (DILI) checklist" provided via the RDC-system/EDC-system. Lab values meeting the hepatic injury definition must always be reported as an AESI. Exemption does not apply.
In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator has to make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist must be followed.

Any DLT:
The following drug related AEs will qualify as a dose limiting toxicity:
For solid tumours patients:
- Any CTCAE grade ≥3 non haematological toxicity considered related to trial medication with the following exceptions:
  - inadequately treated nausea, vomiting or diarrhoea. For fatigue, if present at baseline, there must be an increase of ≥2 grades,
  - electrolytes abnormalities that can be corrected within 72 hours with adequate treatment (in case it occurs, a control should be performed at 72h to determine the 72h duration of the grade 3)
- Any hematologic AE related to the trial medication defined as follows:
  - CTCAE grade ≥4 neutropenia lasting ≥ 7 days (in case it occurs, a control haematology test must be performed at least twice weekly until improvement to a lower grade) and/or complicated by infection, or

- CTCAE grade≥ 4 thrombocytopenia (in case it occurs, a control haematology test must be performed at least twice weekly until improvement to a lower grade), or
- CTCAE grade≥ 3 thrombocytopenia coupled with grade ≥ 2 of bleeding, or
- Febrile neutropenia CTCAE grade 3 (ANC<1000/mm3 and fever ≥ 38.5°C) or higher,

- Any other drug-related AE preventing the patient from taking his treatment according to the given schedule (defined as more than 2 consecutive doses missed during the 21 days of intake of the Cycle for Schedule A or 14 days of intake for Schedule B or during the two times one week of intake of Schedule C or a treatment break between cycles > 14-days in addition to the one week off foreseen in Schedules B and C).

For DLBCL patients:

- Any CTCAE grade ≥3 non haematological toxicity considered related to trial medication with the following exceptions:
  - inadequately treated nausea, vomiting or diarrhoea. For fatigue, if present at baseline, there must be an increase of ≥2 grades),
  - electrolytes abnormalities that can be corrected within 72 hours with adequate treatment (in case it occurs, a control should be performed at 72h to determine the 72h duration of the grade 3)
- Any hematologic AE related to the trial medication defined as follows:
  - CTCAE grade ≥4 neutropenia lasting ≥ 7 days (in case it occurs, a control haematology test must be performed at least twice weekly until improvement to a lower grade) and/or complicated by infection, or
  - CTCAE grade ≥ 4 thrombocytopenia (in case it occurs, a control haematology test must be performed at least twice weekly until improvement to a lower grade), or
  - CTCAE grade≥ 3 thrombocytopenia coupled with grade ≥ 2 of bleeding, or
  - Febrile neutropenia CTCAE grade 3 (ANC<1000/mm3 and fever ≥ 38.5°C) or higher which does not resolve within 48 hours with appropriate treatment (antibiotics, antifungal, antiviral agents and growth factors),
- Any other drug-related AE preventing the patient from taking his treatment according to the given schedule (defined as more than 2 consecutive doses missed during the 14 days of intake in Schedule B which is selected, or treatment break between cycles > 14-days in addition to the one week off foreseen in Schedule B).

For definition of DLT, it is essential that patients are sufficiently treated according to supportive care standards (see 4.2.1). Patients with treatable AEs (nausea, vomiting, and diarrhoea) that are not sufficiently treated do not qualify for DLT and need to be replaced, if this occurs in Cycle 1.
AESIs are to be reported in an expedited manner similar to SAEs, even if they do not meet any of the seriousness criteria – for details please see 5.3.7.

Severity of AEs
The severity of the AE must be classified and recorded in the eCRF according to CTCAE version 4.03 in the eCRF (R10-4848).

Causal relationship of AEs
Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

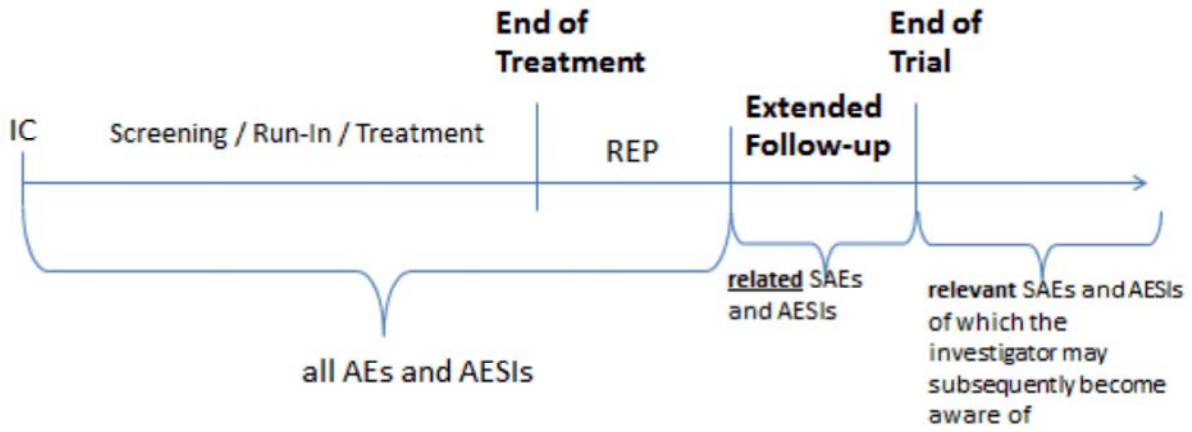
The causal relationship must be provided by the Investigator for all potential trial drugs, i.e. the BI trial drug.

5.3.7 Adverse event collection and reporting

AE Collection
The Investigator shall maintain and keep detailed records of all AEs in their patients' files

The following must be collected and documented on the appropriate eCRF by the Investigator:
- From signing the informed consent onwards through the REP, until the end of the REP:
  - all AEs (non-serious and serious) and all AESIs.
- After the end of the REP until individual patient's end of trial:
  - all related SAEs and all related AESIs.

After the individual patient's end of trial, the investigator does not need to actively monitor the patient for AEs but must only report relevant SAEs and relevant AESIs of which the investigator may become aware of.



- IC = informed consent
- End of treatment = last dose of BI 894999
- REP = residual effect period of 30 days
- End of trial = individual patient's end of trial = last visit mandated per protocol which is the first follow-up if the patient stopped study treatment because of PD or the follow-up at which PD is observed or the decision is taken to start with the next line of cancer treatment or the last ongoing patient has reached the first follow-up at the end of the REP

Figure 5.3.7: 1: Type of AE collection according to trial period

The REP is defined as 30 days after the last trial medication intake. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment please see Section 7.3.4. Events which occurred after the REP will be considered as post treatment events.

AE reporting to sponsor and timelines
The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, by completing and sending the BI SAE form immediately (within 24 hours) to the Sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information, the same rules and timeline apply as for initial information.

Information required
For each AE, the Investigator must provide the information requested on the appropriate eCRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug(s). The Investigator must determine the causal relationship to the trial medication.

The following must also be recorded as an (S)AE in the eCRF and SAE form (if applicable):
- Worsening of the underlying disease (if not part of the exemption as described below) or other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.
  If such abnormalities already pre-exist prior to trial inclusion, they will be considered as baseline conditions.

All (S)AEs, including those persisting after trial completion must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

Pregnancy
In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the Investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the Sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) must be used.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the Sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is

to be completed. If there is an SAE and/or AESI associated with the pregnancy then the SAE and/or AESI has to be reported on the SAE form in addition.
The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

Exemptions to SAE Reporting
Progressive disease (PD) in oncology trials is a study endpoint for analysis of efficacy. PD is exempted from reporting as a (S)AE. Progression of the subject's underlying malignancy will be recorded in the appropriate pages of the eCRF as part of efficacy data collection. Death due to PD is to be recorded on the appropriate eCRF page and not on a SAE form.
Examples of exempted events of PD are:

- Progression of underlying malignancy (PD): if PD is clearly consistent with the suspected progression of the underlying malignancy as defined by the respective response criteria.
- Hospitalization/Procedures due solely to the progression of underlying malignancy (PD)
- Clinical symptoms and/or signs of progression (with or without confirmation by objective criteria e.g. imaging, clinical measurement): if the symptom can exclusively be determined to be due to the progression of the underlying malignancy and does meet the expected pattern of progression for the disease under study.

When there is evidence suggesting a causal relationship between the study drug and the event of progression of the underlying disease, the event must be reported as (S)AE in the eCRF and on a SAE form (if applicable).

The study is monitored by a DMC in order to review data on a regular basis.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of Pharmacokinetics

Standard pharmacokinetic parameters of BI 894999 as listed under secondary [redacted] endpoints will be determined from plasma [redacted] analyses after a single oral dose and after repeated dosing, at steady state along with descriptive statistics. [redacted].
At any time, only in case of drug related grade 3 or grade 4 toxicity, every effort must be made to collect a plasma PK sample; date and time of the sample and of the most recent drug intake (before PK sample) need to be recorded for such samples.

5.4.2 Methods of sample collection

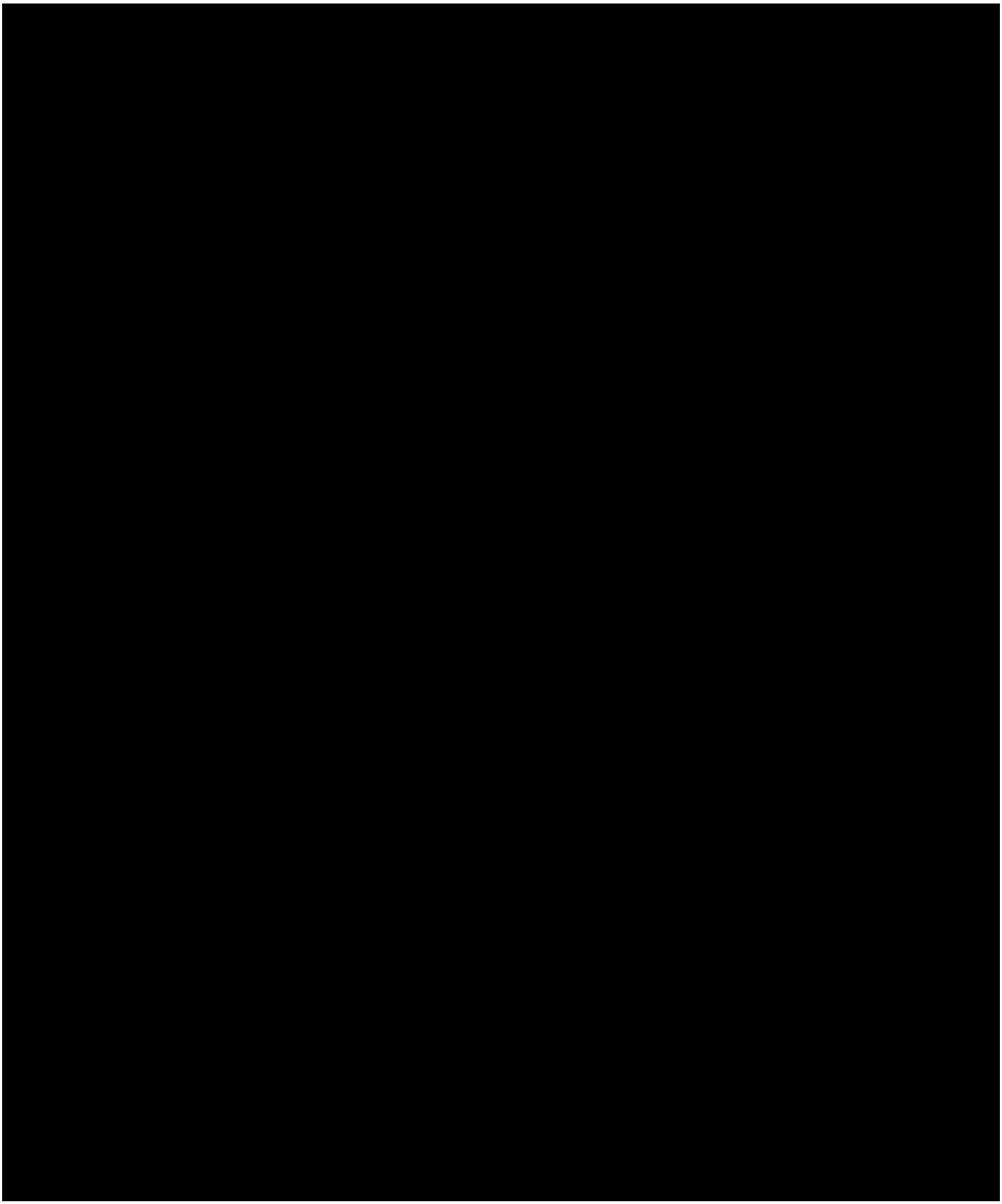
5.4.2.1 Plasma sampling for BI 894999 pharmacokinetics

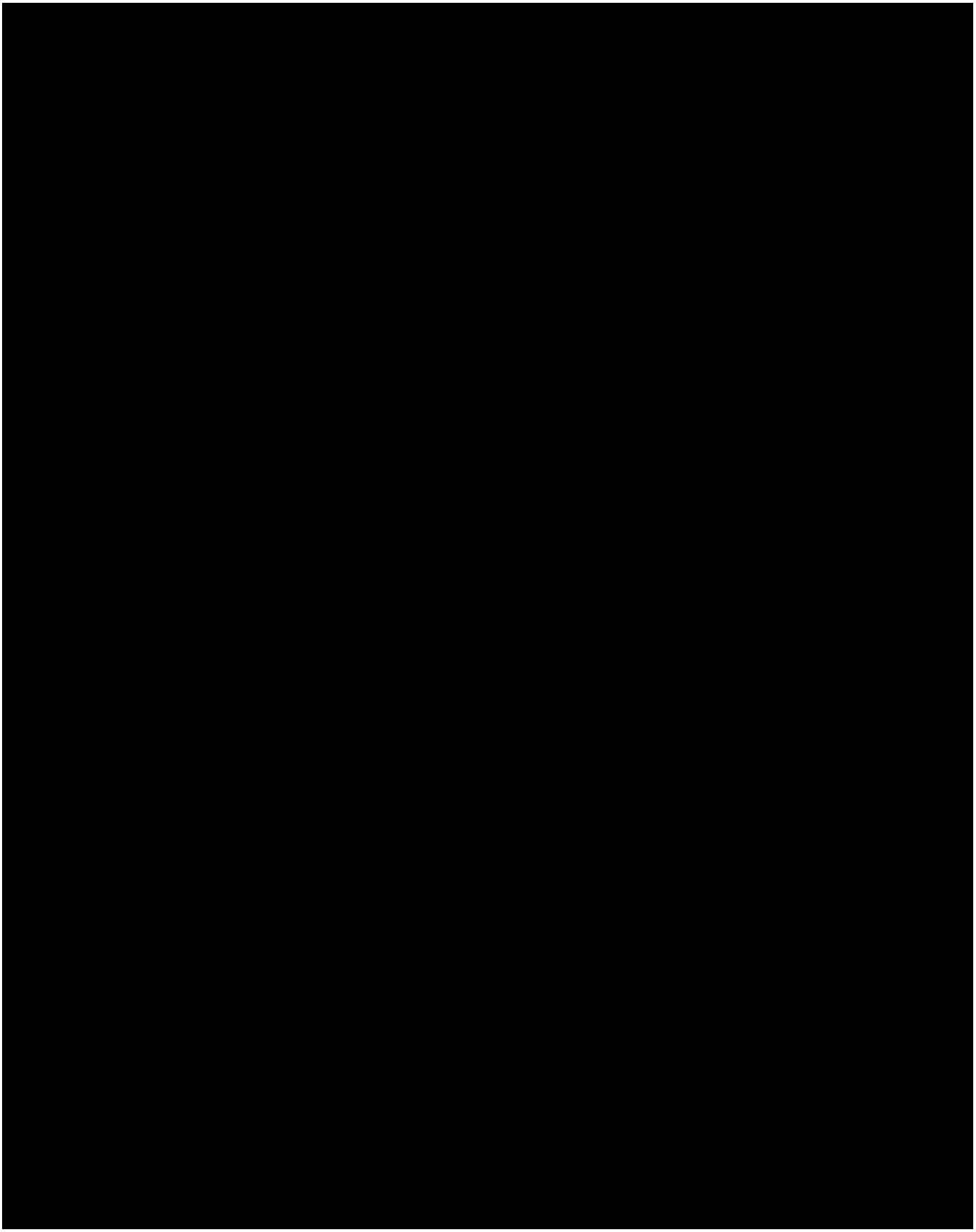
For quantification of BI 894999 plasma concentrations, up to 102 mL blood will be taken from a forearm vein in an EDTA anticoagulant blood drawing tube at the time points specified in the Flow Chart and in Appendix 10.2.

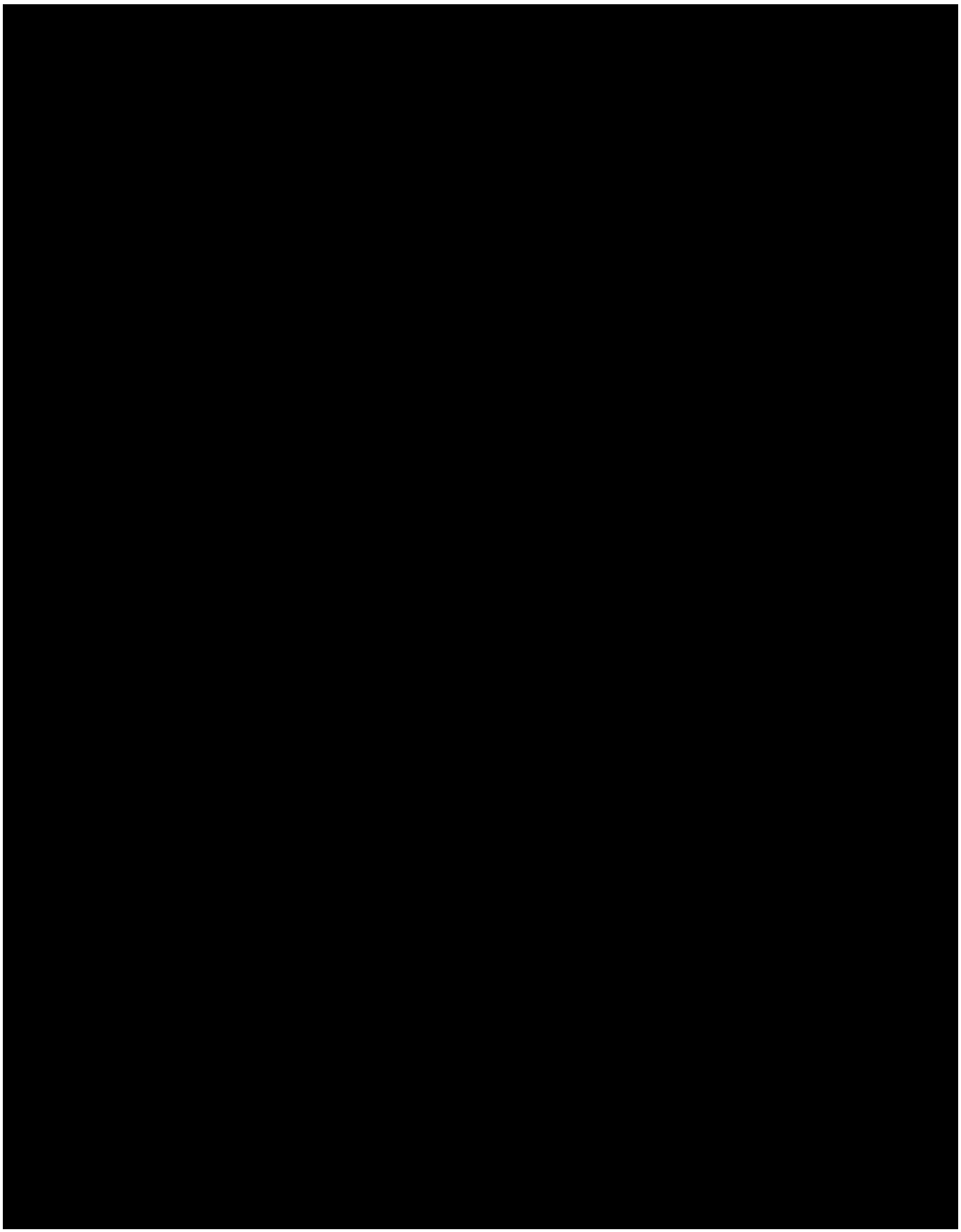
Every attempt must be made to adhere to the time points for the sampling. For the quality of pharmacokinetic analysis, however, the actual times of drug intake and blood sampling as well as of dose administration are crucial. Therefore, exact and actual clock time of BI 894999 intake and blood samplings have to be recorded in the eCRF.
A total of two plasma aliquots will be generated (with about 0.7 mL plasma in each aliquot) from each blood sample. The first aliquot will be used primarily for PK bio-analysis of BI 894999 plasma concentrations, the second aliquot will serve as a back-up sample. The plasma samples (including PK back-up samples) must be stored at about -20°C or below at the clinical site until shipment on dry ice to the bio-analytical laboratory. There, they will also be stored at about -20°C or below until analysis (see Section 5.4.3).
Details on sample collection, preparation of plasma aliquots, handling, storage and shipment are provided in the ISF/laboratory manual.

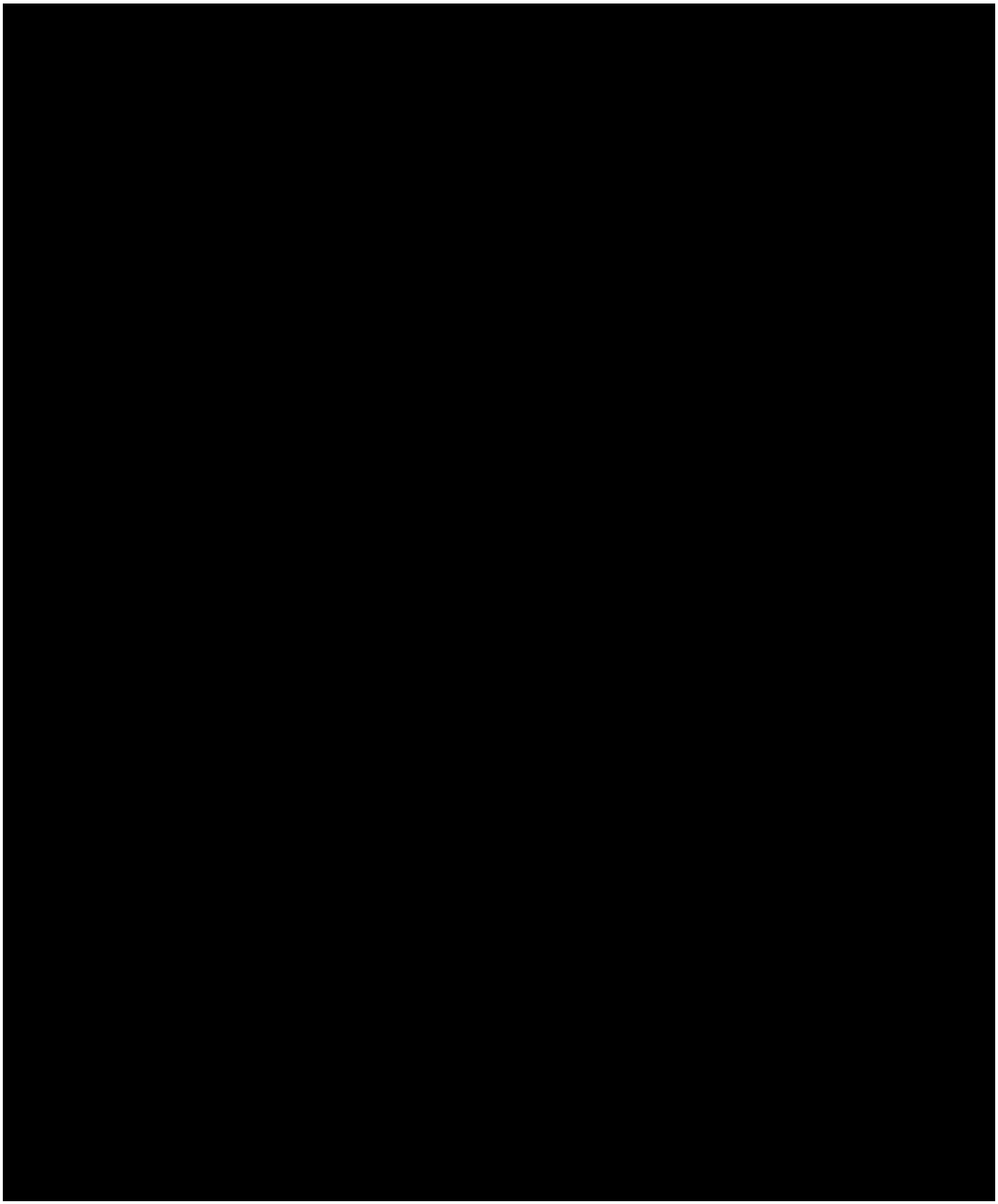
5.4.2.2 Urine sampling and analysis for pharmacokinetics

A blank urine sample will be collected prior to the first drug administration and two 4 mL aliquots retained to check for analytical interference. A protocol start time of -2:00 and a stop time of -2:00 will be used for database setup. All urine voided during the sampling intervals described in Appendix 10.2 will be collected in containers. Patients have to empty their bladder at the end of each sampling interval. The urine weight/volume (weight will be set equal to volume, i.e. 1 kg = 1 L, without correction for specific gravity of urine) for each collection interval will be documented (the weight of the empty and filled container needs to be documented) and two 4 mL aliquots will be stored for bio-analytical measurement. In order to prevent adsorption of BI 894999 it might be necessary to add an additive to the container prior to start of urine collection. The procedure and details will be given in the ISF/laboratory manual.
Until shipment on dry ice to the bio-analytical laboratory, the urine samples will be stored at about -20°C or below at the clinical site and in the same conditions at BI until analysis.
The urine sampling for PK will not happen anymore for the patients recruited under protocol version 12.0 onwards.









[redacted]

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

The endpoints chosen for this study are generally recognized methods of assessing safety and efficacy in oncology studies.
AEs will be graded according to the National Cancer Institute (NCI) CTC AE criteria version 4.03 (R10-4848).
The tumour response will be evaluated by means of the RECIST 1.1 (R09-0262), RECIL 2017 (R17-3378) and PCWG3 (R17-3377) that are well established and scientifically accepted or/and by means of the appropriate tumour marker, depending on the type of cancer.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The study consists of two parts, a dose escalation part (Phase Ia) to determine the MTD in three different Schedules (Schedule A of continuous dosing, Schedule B with an intermittent dosing of 2 weeks on treatment followed by one week break in 3-week cycles, and, starting from protocol version 10.0 onwards, Schedule C with a once daily loading dose on Day 1 followed by 6 days daily intake of a maintenance dose then one week off treatment, repeated every two weeks in 4-week cycles) in patients with solid tumours. The best schedule of administration of BI 894999 in patients with solid tumours was determined between Schedules A and B. The schedule shown to have a more favourable safety, pharmacokinetics and biomarker profile was Schedule B which was chosen to be further investigated in an extension of MTD cohort in patients with solid tumours, to determine the MTD in a DLBCL cohort with extension of this cohort at MTD and in the expansion phase (Phase Ib). In addition, the [redacted] on the pharmacokinetics of BI 894999 was also investigated in some of the patients from the Phase Ia part (around and at MTD), starting in Schedule A and continuing in Schedule B in order to obtain results for at least 12 patients and up to 20 patients. Once MTD was determined for Schedule B in DLBCL patients, MTD will be determined as well with Schedule C in DLBCL patients. Thereafter, the DMC will recommend the best schedule of administration of BI 894999 between Schedules B and C in patients with DLBCL. The schedule shown to have a more favourable safety, pharmacokinetics and biomarker profile will be chosen to be further investigated in an extension of MTD cohort in patients with DLBCL.
The second part (Phase Ib) is an expansion phase to further evaluate safety, efficacy and pharmacokinetics profile of BI 894999 in patients with selected types of solid tumours (SCLC, mCRPC, CRC or NC), as well as biomarker values as a result of treatment with BI 894999 with the selected schedule from Phase Ia, between Schedules A and B, which was B. Once the MTD from Schedule C from Phase Ia was known for patients with solid tumours, the DMC recommended the schedule shown to have a more favourable safety, pharmacokinetics and biomarker profile between B and C. Schedule C was selected, NC cohort with Schedule B was closed to recruitment and NC cohort with Schedule C was opened..

Patients meeting the inclusion and exclusion criteria for the part they are participating in and who have given their written informed consent, are eligible for participation in the study.
Patients will visit the clinical site at the time points specified in the Flow Chart for the appropriate Schedule of dosing they are entering (see also Appendix 10.4 for a complete list).
In situations where a patient is unable or unwilling to attend a clinic visit, the Investigator must assess the benefit-risk balance for the individual patient and may decide to perform a visit remotely if this is in the best interest of the patient and if agreed with the Sponsor, provided that it is allowed by local country regulations and the investigator ensures that the local facilities are adequately qualified to perform the tests required per protocol for the given visit.
If a patient misses a scheduled visit, and the patient reports to the investigator between the missed visit and the next scheduled visit, the missed visit must be done with the actual date and the reason must be given for the delayed visit.
For the biopsies and PK sampling procedures of Cycle 1, the patient must however still be under treatment and not in a treatment break period to perform the evaluations foreseen during

the missed visit. The next visit must then take place at the scheduled time after the first administration of the trial drug in the respective treatment cycle.

Once the decision for any reason is taken for a patient to stop the treatment with BI 894999, an EOT visit must occur as soon as possible.
After the EOT visit, the patient must undergo a follow-up evaluation during an EOR visit (or at least a phone contact if a visit is not possible), 30 days (+ 7 days) after the last BI 894999 intake.
If the patient was not discontinued because of withdrawal of consent, disease progression, treatment with another anti-cancer drug, loss to follow-up or because of the end of the trial, he/she must continue to undergo follow-up visits every 12 weeks until disease progression, lost to follow-up, treatment with another anti-cancer therapy or end of the trial. For NC patients, the survival status will be collected for all patients until death, lost to follow-up or until 12 months after the end of the trial, according to their consent, after approval of protocol version 11.0.

The study will be conducted according to the principles of Good Clinical Practice (GCP).

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The procedures required at each study visit in both phases are presented in the appropriate study Flow Charts for the Schedule of this protocol and are detailed per visit in Appendix 10.4.
Listed below are the key procedures required:

- PK samples during Cycle 1 at Visits 1, 2, 3 and 4 in Schedule A or during Cycles 1-2 in Schedule B or during Cycle 1 at Visits 1, 2, , 4 and 5 in Schedule C (not anymore at Visits 2 and 3 for NC and DLBCL patients starting from protocol version 12.0)
- Registration of all AEs occurring after the Informed Consent Form (ICF) has been signed and until the end of the REP
- Baseline and on treatment, in Cycle 1 for the three Schedules and in Cycle 2 for Schedule B whole blood biomarkers assessments and tumour biopsies biomarkers assessments (only when opted for in the escalation phase and in the expansion phase)
- Tumour assessment (based on CT and/or MRI scan according to RECIST 1.1 in patients with solid tumours including mCRPC patients with measurable disease according to RECIST 1.1, or based on FDG-PET/CT scans according to RECIL 2017 (R17-3378) in DLBCL patients or based on bone scan and PSA level according to PCWG3 (R17-3377) in mCRPC patients of Phase Ib without measurable disease according to RECIST 1.1) must be performed once every 2 cycles (meaning every 6 weeks for Schedules A and B, every 8 weeks for Schedule C, if no delays in cycles but as close as possible to end of the second of the two cycles of treatment if there was a delay), in DLBCL every 2 cycles until Cycle 4, every 4 Cycles thereafter, every 4 cycles in mCRPC patients) after start of BI 894999.
- LVEF assessment at screening, at the end of Cycle 2 during the treatment period as well as at the EOT if not performed within the last 6 weeks before and if the patient's health status allows.

6.2.1 Screening period

Screening Period
The screening period may run over a period of 28 days (period within the trial and before the very first intake of BI 894999). For the detailed description of the tests to be performed during this period, please refer to Appendix 10.5.1.

Baseline Conditions
Demographics (sex, birth date, race and ethnicity where allowed), information on smoking and alcohol history, and baseline conditions will be collected during the screening visit.

Medical History:
History of cancer will also be obtained.

For solid tumours, the type of cancer, the date of the first histological diagnosis (month and year may be sufficient), and the primary tumour site will be reported on the eCRF. The differentiation grade (not specified, undifferentiated, poorly differentiated, moderately differentiated, well differentiated) obtained at the time of diagnosis and the location of metastatic sites as well as the stage according to the tumour, (lymph) node, metastasis (TNM) classification will be provided as obtained at diagnosis and at study screening. Previous surgeries will be reported. For NUT carcinoma patients entered into the trial, the methodology implemented to diagnose NC, the NUT fusion partner, and the threshold for a positive NC will be recorded in the eCRF.
For DLBCL, the date of first histological diagnosis (month and year may be sufficient), the staging according to revised Ann Arbor staging system as proposed by Cheson et al (R14-3387), (see Table 6.2.1: 1 the immunohistochemical cell of origin (COO) information, the double-hit lymphoma (DHL) or the double expressor lymphoma (DEL) status should be documented.

Table 6.2.1: 1 Revised Ann Arbor staging (R14-3387)

Revised Staging System for Primary Nodal Lymphomas		
Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.
*Whether stage II bulky disease is treated as limited or advanced diseasemay be determined by histology and a number of prognostic factors

Previously administered chemotherapy, tyrosine kinase inhibitors treatment, vaccine-therapy, antibodies therapy, immune-therapy, and hormone-therapy will be reported including start and end dates (month and year may be sufficient), as well as whether therapy was given as neo-adjuvant, adjuvant, curative or palliative therapy.

Concomitant therapies
Relevant concomitant diagnoses and/or therapies present at study entry and/or during screening and relevant to the patient's safety during the study as judged by the investigator will be recorded in the eCRF.

6.2.2 Treatment period(s)

Please refer to Appendix 10.5.2 for a detailed description of each visit during the treatment period.

6.2.3 Follow Up Period and Trial Completion

6.2.3.1 End of treatment (EOT) visit

The EOT visit will be performed after permanent discontinuation of trial medication for any reason, as soon as possible but no later than 7 days after permanent discontinuation of the trial medication or when the investigator decided with the patient to permanently discontinue the trial medication or became aware that the trial medication had been terminated.

The assessments of the EOT visit will then be performed instead of the next planned visit. For NC patients, overall clinical benefit based on investigator's judgement will also be recorded (see Section 5.2.1).

If the patient finishes active treatment without having progressive disease, tumour assessment/imaging must be performed at the time of treatment discontinuation, unless it has been done within the past 6 weeks. If active treatment is stopped due to progressive disease, then imaging must be performed at the point in time when progression is first noted irrespective of when the most recent imaging was done.

6.2.3.2 Follow-up visits

The REP is defined in Section 5.3.7. The first follow-up visit corresponds to the End of REP (EOR) visit and may not be performed earlier than 30 days after permanent discontinuation of the trial medication. The information collected at this visit must include all new AEs that occurred after EOT and a follow-up of AEs ongoing at EOT.

Additional follow-up visits after the EOR visit will only be performed for patients who did not progress on treatment, once every 12 weeks (at least by telephone) until disease progression, introduction of a new anti-cancer treatment, death, loss to follow-up or end of the whole trial as specified in Section 8.6.

A patient will be considered as having completed the study if he/she discontinues because of disease progression and has performed the EOR visit 30 days after EOT or was lost to follow-up or withdrew consent for further evaluation at the EOT visit. If the patient discontinues for any other reason, he/she will be considered as withdrawn.

For NC patients, after approval of protocol version 11.0, the overall survival status will be collected, according to patient's consent, until death, loss to follow-up, withdrawal of consent to be further followed-up or until 12 months after the end of the whole trial.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a Phase I, open-label, dose-escalation trial to determine the MTD for three Schedules of BI 894999 in patients with solid tumour and for Schedule B and Schedule C in the DLBCL cohort and also to assess the safety profile, PK/pharmacodymamics biomarkers, and anti-cancer activities of BI 894999.

Phase Ia:

The objective of the Phase Ia is to determine the MTD, defined as the highest dose with less than 25% risk of the true DLT rate being above 33%, separately for three Schedules of BI 894999 in patients with solid tumour and for the Schedules B and C in the DLBCL cohort. Dose escalation and determination of MTD for Schedule A and Schedule B will be guided by a Bayesian 2-parameter logistic regression model with overdose control (R13-4803; R13-4806). Dose escalation and MTD determination for Schedule C will be guided by a Bayesian 5-parameter logistic regression model with overdose control (R15-4233), which is described in statistical appendix section 10.3.2. These designs have been shown to be superior regarding the precision of MTD determination compared to 3+3 designs.

The Bayesian 2-parameter logistic regression model (BLRM) is formulated as follows:
$\text{logit}(p(d)) = \log(\alpha) + \beta \times \log(d/d^*)$,
where $\text{logit}(p) = \log(p/(1-p))$.
$p(d)$ represents the probability of having a DLT in the first cycle at dose d, $d^* =$ 80 mg is the reference dose, allowing for the interpretation of α as the odds of a DLT at dose d^*, and $\theta = (\log(\alpha), \log(\beta))$ with $\alpha, \beta > 0$ is the parameter vector of the model.

Since a Bayesian approach is applied, a prior distribution $\pi(\theta)$ for the unknown parameter vector θ needs to be specified. This prior distribution used in the BLRM for the dose escalation of Schedule A will be specified as a mixture of three multivariate normal distributions, i.e.
$\pi(\theta) = \varphi_1\pi_1(\theta) + \varphi_2\pi_2(\theta) + \varphi_3\pi_3(\theta)$

with
φ_i, i = 1, 2, 3 the prior mixture weights ($\varphi_1 + \varphi_2 + \varphi_3 = 1$)

and
$\pi_i(\theta) = \text{MVN}(\mu_i, \Sigma_i)$

the multivariate normal distribution of the i-th component with mean vector μ_i and covariance matrix Σ_i, with

$$\Sigma_i = \begin{pmatrix} \sigma_{i,11}^2 & \sigma_{i,11}\sigma_{i,22}\rho_i \\ \sigma_{i,11}\sigma_{i,22}\rho_i & \sigma_{i,22}^2 \end{pmatrix}$$

Mixture prior distributions have the advantage that they allow for specification of different logistic dose-toxicity curves, therefore making the prior more robust.

Initial prior derivation

For the current study of Schedule A dose escalation, no relevant information in the form of human data is available, since no study in a comparable population has been conducted. Therefore, the three mixture components were established as follows:

1. A weakly informative prior was derived to reflect a priori assumption that the median DLT rate at the starting dose of 0.2 mg would equal 1%, and the median DLT rate at 80 mg would equal 40%. This yields $\mu_1 = (-0.402, -0.350)$. The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{1,11} = 2$, $\sigma_{1,22} = 1$ and $\rho_1 = 0$, respectively. The prior weight φ_1 for the first component was chosen as 0.9.
2. A high-toxicity weakly informative prior was derived to reflect the case that the compound would be much more toxic than expected. For this prior component, it was assumed that the median DLT rate at the starting dose of 0.2 mg would equal 10%, and the median DLT rate at 80 mg would equal 60%. These assumptions yield $\mu_2 = (0.409, -0.826)$. The standard deviations and correlations were set identical to the weakly informative prior, i.e. $\sigma_{2,11} = 2$, $\sigma_{2,22} = 1$ and $\rho_2 = 0$, respectively. The prior weight φ_2 for the second component was chosen as 0.05.
3. A low-toxicity weakly informative prior was derived to reflect the case that the compound would be much less toxic than expected. For this prior component, it was assumed that the median DLT rate at the starting dose of 0.2 mg would equal 0.1%, and the median DLT rate 80 mg would equal 5%. These assumptions yield $\mu_3 = (-2.936, -0.413)$. The standard deviations and correlations were set to $\sigma_{3,11} = 5$, $\sigma_{3,22} = 0.01$, therefore almost fixing the slope parameter to its mean. The correlation was set to 0, i.e. $\rho_3 = 0$. The prior weight φ_3 for the third component was chosen as 0.05.

A summary of the prior distribution used in the BLRM for Schedule A dose escalation is provided in Table 7.1:1. Additionally, the prior probabilities of DLT at different doses, as well as the corresponding probability of under-, targeted and overdosing, are shown in Table 7.1: 2. Graphically, the prior medians with accompanying 95% credible intervals are shown in Figure 7.1: 3. As can be seen from both the Table and the Figure, the prior medians of the DLT probabilities are in-line with the prior medians derived from the weakly informative prior, and the uncertainty around the medians is large, showing the low amount of information this prior provides. This is also supported by the prior sample size, i.e. the information contained in the prior. This is approximately equal to 1.22 patients, i.e. less than or around half of the weight the first cohort in the study will have.

Table 7.1: 1 Summary of prior distribution

Prior Component	Mixture Weight	Mean vector	SD vector	Correlation
1: Weakly inf.	0.900	(-0.402, -0.350)	(2.000, 1.000)	0.000
2: High Tox	0.050	(0.409, -0.826)	(2.000, 1.000)	0.000
3: Low Tox	0.050	(-2.936, -0.413)	(5.000, 0.010)	0.000

Table 7.1: 2 Prior probabilities of DLT at selected doses

Dose	Probability of true DLT rate in					Quantiles		
	[0–0.16)	[0.16–0.33)	[0.33–1]	Mean	SD	2.5%	50%	97.5%
0.2	0.815	0.073	0.112	0.102	0.203	<0.000	0.007	0.793
0.5	0.784	0.083	0.134	0.119	0.218	<0.000	0.012	0.830
1.0	0.755	0.090	0.155	0.136	0.231	<0.000	0.020	0.855
2.5	0.704	0.108	0.188	0.164	0.249	<0.000	0.036	0.885
5	0.659	0.117	0.224	0.191	0.263	<0.000	0.058	0.904
10	0.597	0.134	0.269	0.226	0.278	<0.000	0.092	0.924
20	0.513	0.156	0.331	0.273	0.293	<0.000	0.150	0.941
40	0.407	0.171	0.422	0.339	0.306	0.001	0.243	0.958
80	0.280	0.165	0.555	0.435	0.317	0.005	0.395	0.974
120	0.219	0.148	0.633	0.499	0.324	0.007	0.502	0.986

Doses printed in bold face meet the overdose criterion (P (overdose) < 0.25)

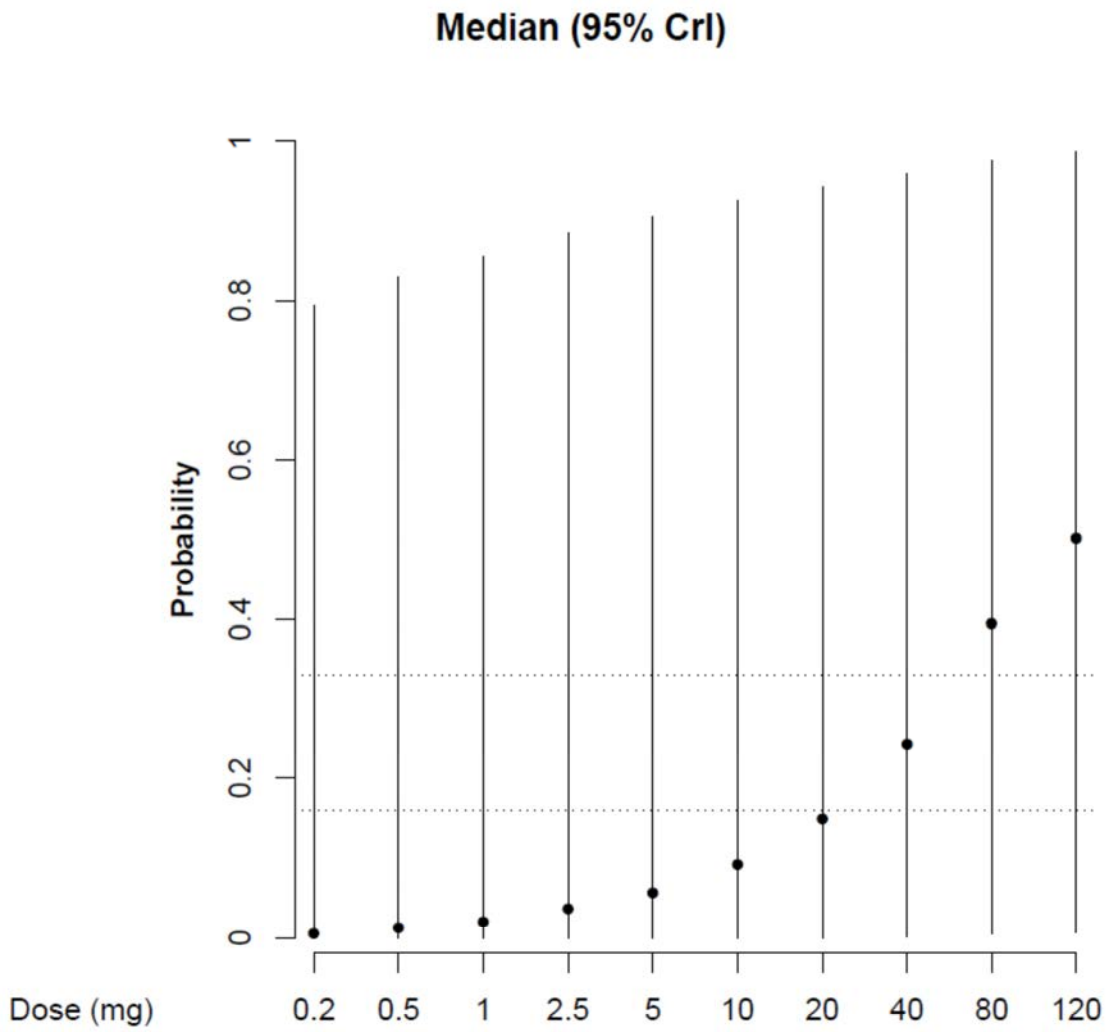


Figure 7.1: 3 Prior medians and 95% credible intervals

The priors may be updated once the trial has started in case new data that can be used will be available. After the initial prior derivation the five different BLRM models used for the dose finding of Schedule A in patients with solid tumour, of Schedule B in patients with solid tumour, of Schedule C in patients with solid tumour, of Schedule B in patients with DLBCL, and of Schedule C in patients with DLBCL will be handled separately.

For Schedule A and Schedule B, the MTD may be considered reached if the following criteria are fulfilled (for Schedule C, see Section 10.3.2)

1. At least 1 DLT on the trial and either
2. At least 6 patients have been treated at the MTD and the posterior probability of the true DLT rate in the target interval (16%-33%) is above 50% for Schedule A dose escalation / >

60% for Schedule B dose escalation in solid tumour and the DLBCL dose escalation (due to the fact that an updated prior based on observed safety data from Schedule A dose escalation is used for the Schedule B dose escalation in solid tumour and DLBCL dose escalation), OR

3. At least 12 patients in each schedule in solid tumours and in Schedule B in the DLBCL indication with 6 patients having been treated at MTD for each MTD determination.

Statistical model assessment

The model was assessed using two different metrics:

1. Hypothetical data scenarios: for various potential data constellations as they could occur in the actual trial, the maximal next doses as allowed by the model and by the 100% escalation limit are investigated. Data scenarios thus provide a way to assess the "on-study" behaviour of the model.
2. Simulated operating characteristics: these illustrate for different assumed true dose-toxicity relationships, how often a correct dose would be declared as MTD by the model. They are a way to assess the "long-run" behaviour of the model.

In summary, the model showed very good behaviour as assessed by these metrics. More details can be found in Section 10.3. The simulations for scenarios and operating characteristics were produced using R version 3.0.3.

With the addition of Schedule B and Schedule C in patients with solid tumour and Schedule B and Schedule C in the DLBCL cohort after the start of Schedule A in patients with solid tumour, the initial priors used in the Bayesian logistic regression model were updated based on the cumulatively observed data. For Schedule C, loading dosing and maintenance dosing will be treated as a combination of BI 894999. The initial priors for maintenance dosing are updated based on the observed data from Schedule A and B in patients with solid tumour. More details can be found in Section 10.3 and TSAP.

Phase Ib:

The expansion Phase Ib will recruit a minimum of 9 patients and a maximum of 20 patients with measurable disease according to RECIST 1.1 (mCRPC patients with no measurable-disease are eligible according to PCWG3 criteria (see 3.3.2.1) to the dose and Schedule recommended by the DMC for Phase Ib part (based on MTD) per type of tumour (SCLC, mCRPC or CRC) selected by the DMC. For NC patients, up to 40 patients will be recruited with Schedule B and/or with Schedule C.

Five patient cohorts are considered in the Phase Ib part of this study. To effectively use the information from these 5 patients' cohorts in the assessment of the efficacy of BI 894999, a 2-stage Bayesian hierarchical model (BHM) approach, which assumes full exchangeability of model parameters and allows borrowing information across patients' cohorts, will be used to analyse the response rate endpoints (i.e. objective response rate, disease control rate). The BHM has 2 main components: a data model and a parameter model. The data model is a binomial sampling model

$$r_j \mid n_j \sim \text{Binomial}(\pi_j, n_j),\ j = 1, 2, 3, 4, 5$$

where n_j and r_j are the number of patients and the corresponding number of patients with response in each patient cohort. The parameter model for the exchangeable log-odds parameters $\theta j = \log(\pi_j / (1 - \pi_j))$ is specified as

$$\theta_j \mid \mu, \tau \sim N(\mu, \tau^2), j = 1, 2, 3, 4, 5$$

where μ denotes the "overall" mean and τ determines the inter-cohort heterogeneity. A non-informative (improper) uniform prior is used for the main parameter μ. For the inter-cohort heterogeneity parameter τ, a half-normal prior with scale parameter 100 is used which is a very conservative assumption regarding between-cohort variability and hence leads to only little borrowing of data across patient cohorts because there is little prior information on the strength of the correlation between the treatment effects across the 5 cohorts.

In stage 1 of the Phase Ib part, approximately 9 patients will be enrolled and treated in each of the SCLC, mCRPC and CRC cohorts. If no objective response is observed out of the approximate 9 patients in a patient cohort, this cohort will be closed for stage 2 recruitment. Analysis of stage 1 may be performed for each cohort separately. At the end of stage 2 of the Phase Ib part, the BHM approach will be used to estimate the shrinkage estimator of θ_j for each patient cohort and the response data from the DLBCL MTD extension cohort will also be considered in the shrinkage estimator of θ_j. Since the full exchangeability assumption may not hold for the BHM, the exchangeability-non exchangeability (R17-3435) approach will also be applied as a sensitivity analysis of the response rate endpoints in the Phase Ib part.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No formal hypothesis testing is planned in this trial. This is an exploratory Phase Ia/Ib study with the main objective of dose escalation and MTD determination (for Phase Ia part) and safety and efficacy evaluation (for Phase Ib part). All analyses in this trial are descriptive and exploratory by nature.

7.3 PLANNED ANALYSES

Only one analysis population will be considered for efficacy and safety analyses: the treated set. The treated set (TS) will consist of all patients who were treated with any dose of BI 894999. Patients will be analysed under the actual treatment received on Day 1.

The PK set includes all subjects in the TS who provide at least one observation for at least one PK endpoint without important protocol violations relevant to the evaluation of PK.

[redacted]

The primary analysis will be based on the treated set population excluding patients that have to be replaced for analysis of the MTD, see Section 3.3.4.1 for further details.

No per protocol population will be used for analyses; however important protocol violations will be identified and listed.

7.3.1 Primary endpoint analyses

In order to determine the MTD, the occurrence of DLTs in the first cycle will be assessed on an individual patient level in Phase Ia part. The MTD will be determined as described in Section7.1 for Schedules A and B in patients with solid tumour and in Section 10.3.2 for Schedule C. The description for MTD determination for Schedule B and Schedule C in the DLBCL cohort can be found in Section 7.1.

Based on the data observed in the trial, other models might be considered either additionally or replacing the primary model. For feasibility or other reasons, a different dose might be considered as the recommended dose for Phase Ib.
The number of patients with DLTs that occurred during the first treatment cycle (first 21 days for Schedules A and B, first 28 days for Schedule C) in Phase Ia part and during the entire treatment period in Phase Ib part of this study will be summarized separately. For Phase Ia part of this study, the number of patients with DLTs during the first cycle will be summarized by dose level for each schedule (A, B and C) in solid tumour and for Schedule B and Schedule C in the DLBCL cohort. For the Phase Ib part of this study, the number of patients with DLTs during entire treatment period will be summarized by different cohorts and the BLRM will be rerun to re-evaluate the MTD together with all relevant data collected in Phase Ib.

7.3.2 Secondary endpoint analyses

Descriptive analyses will be conducted for secondary endpoints.

Number of DLTs

The number of DLTs occurred during the entire treatment period in Phase Ia part of this study will be summarized by dose level for each schedule (A, B and C) in solid tumour and for Schedule B and Schedule C in the DLBCL cohort.

Secondary efficacy analyses

Objective response and best overall response assessed by the investigator according to RECIST version 1.1 for solid tumour in each schedule, or using RECIL 2017 for the DLBCL patients or via bone scan in combination with PSA evaluation, as well as the PSA responder rate will be analysed descriptively for each schedule in solid tumour and for Schedule B and Schedule C in the DLBCL cohorts. The number of patients with objective response and with best overall response will be summarized separately for the Phase Ia part and the Phase Ib part. For the Phase Ia part, frequency distribution and descriptive statistics will be provided by dose level for each schedule in solid tumour and for Schedule B and Schedule C in the DLBCL cohorts. For the Phase Ib part, a Bayesian hierarchical modelling approach will be used to derive the shrinkage estimators of the response rate endpoints of each patient cohort together with the 95% credible interval. The MTD extension cohort of the DLBCL cohort will also be considered in the BHM of the shrinkage estimators of the response rate endpoints. In addition, the frequency distribution and descriptive statistics will also be provided for each patient cohort. A sensitivity analysis using the EXNEX method may also be conducted to account for non-exchangeability of the response rates across patient cohorts.

For PFS to be assessed for the Phase Ib part of this study, if a patient did not die or progress until the last visit in the study, this patient will be censored at the last time point known to be alive and progression-free. Kaplan-Meier method will be used to analyse PFS.
For patients with 'event' as an outcome for PFS:
• PFS [days] = date of outcome – date of the first treatment administration + 1.
For patients with 'censored' as an outcome for PFS:
• PFS (censored) [days] = date of outcome – date of the first treatment administration + 1.

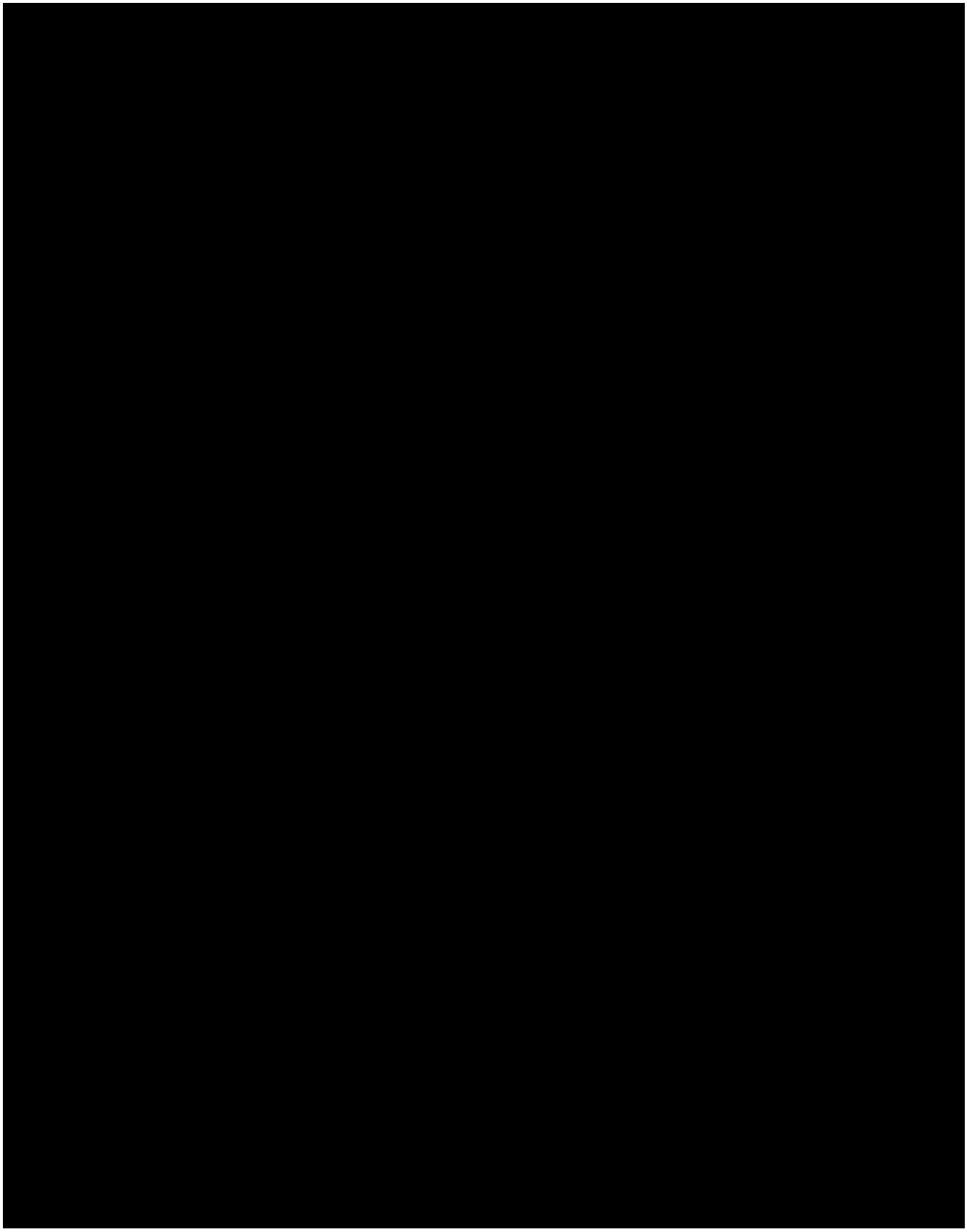
For NC patients, overall survival is a secondary endpoint, defined as the time from the first treatment administration to the date of death. OS will be analysed descriptively by Kaplan-Meier method.
For patients with 'event' as an outcome for overall survival:
• Overall survival [days] = date of death – date of the first treatment administration + 1.
For patients with 'censored' as an outcome for overall survival:
•Overall survival (censored) [days] = date of outcome – date of the first treatment administration + 1.

[redacted]

[redacted]

Details of analysis of PK endpoints and other efficacy endpoints will be provided in the TSAP.

[redacted]



[redacted]

7.3.4 Safety analyses

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All AEs with an onset between start of treatment and end of the REP, a period of 30 days after the last dose of trial medication, will be assigned to the treatment period for evaluation under the treatment received on Day 1. The actual treatment at AE onset will be displayed in subject data listings.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.
Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs. To this end, all AEs occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'. The residual effect period is defined as 30 days after the last trial medication intake. AEs that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.3.5 Pharmacokinetic analyses

For pharmacokinetic analysis and displays, concentrations will be used in the same format as reported in the bio-analytical report. Only concentrations within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. For derivation of pharmacokinetic parameters see Appendix 10.1.

Non-compartmental pharmacokinetic analyses of the plasma concentration-time data will be performed using a validated software program (WinNonlin®Phoenix, current version) and for this purpose the actual sampling time for pre-dose samples will be set to zero.
Plasma concentrations will be plotted graphically versus time for all subjects as listed in the drug plasma concentration-time tables. For the presentation of the mean profiles, the arithmetic and geometric mean and the planned blood sampling times will be used. If the actual sampling

time deviates significantly from the planned time, the corresponding plasma concentration will be excluded from the calculation of descriptive statistics.

[redacted]

[redacted]

[redacted]

[redacted]

7.4 INTERIM ANALYSES

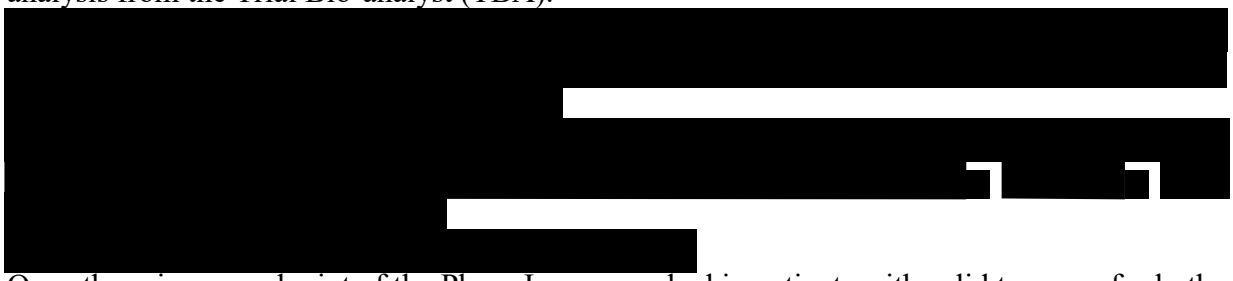
Interim safety evaluations will be performed as considered necessary. In particular safety evaluations will be performed after each dose cohort by the DMC consisting of the investigators and representatives of the sponsor (refer to Section 3.1.1). Based on this, the DMC will recommend the next dose level as well as the corresponding cohort size. DMC meeting minutes and outputs provided for these DMC meetings will be documented and archived in the TMF.

In the Phase Ib part of this study, an interim futility assessment will be conducted after approximate 9 patients are enrolled and evaluable for tumour response evaluation by imaging in each of the SCLC, mCRPC and CRC patients' cohorts. If no objective response is observed in any of the patients in a cohort, this patient cohort will be closed for further enrolment. These futility assessments may be performed separately for each cohort.

[redacted]

Unblinded preliminary exploratory PK analysis of BI 894999 and pharmacodynamics analyses will be performed each time it will be deemed necessary by the trial team and DMC to investigate the PK and pharmacodynamics characteristics of BI 894999.

The TCPK will receive the bio-analytical results to be able to perform the exploratory PK analysis from the Trial Bio-analyst (TBA).



Once the primary endpoint of the Phase Ia was reached in patients with solid tumours for both schedules A and B, and the MTD was confirmed in the extension cohort with the selected schedule (B) in these patients, a Phase Ia report was prepared based on the Phase Ia data for patients with solid tumours in Schedules A and B. For this purpose, a database snapshot was performed. A summary of safety and efficacy endpoints and determination of the recommended Phase Ib dose and schedule was included in the Phase Ia report. The Phase Ia report is made available for all investigators who participate in the Phase Ib. Once MTD in Schedule C will be determined and confirmed in the extension cohort, the report for Schedules A and B in solid tumours together with the results for Schedule C will be the basis for publication by the Coordinating Investigator. Prior to initiation of Phase Ib, relevant data from the Phase Ia part for Schedules A and B will also be sent to regulatory agencies in the countries where Phase Ia Schedules A and B took place and where Phase Ib will take place.

7.5 HANDLING OF MISSING DATA

Missing baseline laboratory values will be imputed by the respective values from the screening visit. No other imputations will be performed on missing data and every effort will be made to obtain complete information on all AEs with particular emphasis on potential DLT and to follow-up the patients for efficacy data.

7.5.1 Plasma concentration - time profiles

Concentration data identified with NOS (no sample), NOR (no valid result), NOA (not analysed), BLQ (below the limit of quantification), and NOP (no peak detectable) will be ignored and not replaced by zero at any time point (applies also to the lag phase including the pre-dose value). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the "2/3 rule" is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e. BLQ, NOR, NOS, NOA, NOP are included).

7.5.2 Pharmacokinetic parameters

In the noncompartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. BLQ and NOP values in the lag phase will be set to zero. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ/NOP values of the profile will be ignored. If the pre-dose concentration is less than or equal to 5% of C_{max} value in that subject, the subject's data

without any adjustments can be included in all pharmacokinetic measurements and calculations (i.e. the pre-dose value will not be changed to zero). If the pre-dose value is greater than 5% of C_{max}, the subject should be dropped from all statistical evaluations. The individual pharmacokinetic parameters can be calculated and listed separately. Every effort will be made to include all concentration data in an analysis. If not possible, a case to case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

• If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g. descriptive statistics) and for graphical presentation.
• If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However the excluded concentration itself will be listed in the clinical trial report associated with an appropriate flag.
Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated".

7.6 RANDOMISATION

Patients will be assigned, not randomised, into escalating dose cohorts by order of admission into the trial. Doses will be assigned based on the decision made by the DMC (see Section 7.3.4).

7.7 DETERMINATION OF SAMPLE SIZE

About 104 patients are expected for the Phase Ia dose escalation part:

- 47 patients were included for both Schedules A and B in patients with solid tumours including a total of 12 patients in the MTD cohort of solid tumours for the selected schedule between A and B (B) (refer to Table 10.3.1: 3)
- approximately 34 patients in the DLBCL cohort: 14 patients were included to determine the MTD in Schedule B, 12 patients are expected to be necessary to determine the MTD in Schedule C and 6 up to 8 patients to confirm the MTD in the schedule selected by the DMC (B or C).
- Approximately 23 patients for Schedule C in patients with solid tumours (16 were necessary for MTD determination and an addition of 7 patients to confirm the MTD)

Fewer or more patients might be needed for the Phase Ia part based on the recommendation of the DMC and the criteria specified (see Section 7.1).

[redacted]

About 80 up to100 patients are expected for the Phase Ib expansion part:
Additional minimum 9 evaluable patients will be included in the Phase Ib expansion phase for each type of solid tumour (SCLC, mCRPC or CRC). If at least 1 out of 9 evaluable patients in a

given cohort has an objective response, the cohort would be further extended up to 20 patients. The 3 cohorts recruited respectively 12, 11 and 14 patients to reach the minimum of 9 evaluable patients. The cohorts of CRC, mCRPC and SCLC didn't pass the futility. 20 patients with NC were recruited in Schedule B. Since Schedule C was selected after MTD determination of Schedule C in phase Ia solid tumour patients as recommended by DMC, the NC cohort with Schedule B was closed and the NC cohort with Schedule C is recruiting up to 40 patients.

Different homogeneous scenarios and heterogeneous scenarios are considered in the simulations to assess the frequentist operating characteristics of the BHM approach for the Phase Ib part of the study. The simulation results as shown in Table 7.7: 1 below show that, with the proposed maximum cohort size of 20 patients and an interim futility assessment after 9 patients in each patient cohort in the SCLC, CRPC and CRC cohorts, the BHM approach has high probability of making the correct decision under a wide range of scenarios of both complete exchangeability assumption and some "nugget" scenarios.

Table 7.7: 1 Operating characteristics of the Bayesian Hierarchical Modelling approach used in the Phase Ib part of this study under different scenarios

Scenario (objective response rate (%) in each patient cohort)	Probability of shrinkage estimator of the objective response rate ≥20% in at least one cohort	Probability of shrinkage estimator of the objective response rate ≥20% in each cohort	Average total sample size
30 / 30 / 30	0.99	0.92 / 0.94 / 0.94	59
25 / 25 / 25	0.94	0.74 / 0.74 / 0.80	58
10 / 10 / 10	0.16	0.09 / 0.08 / 0.07	47
5 / 5 / 5	0.04	0.02 / 0.02 / 0	38
10 / 10 / 30	0.81	0.24 / 0.22 / 0.74	51
5 / 5 / 30	0.84	0.07 / 0.08 / 0.83	45
10 / 30 / 30	0.97	0.50 / 0.89 / 0.89	55
5 / 30 / 30	0.98	0.57 / 0.86 / 0.89	52

20 patients in each cohort with interim futility assessment after 9 patients in each cohort. Number of simulations = 100

Therefore, a total sample size of approximately 196 patients is expected for this study.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for GCP and relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014 and the US FDA regulations.
For each US site / investigator incorporated under a US IND, the US IND requirements outlined in the US Code of Federal Regulations must also be met and a Form FDA 1572 needs to be filled in.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The Investigator will inform the Sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

The rights of the Investigator and of the Sponsor with regard to publication of the results of this trial are described in the Investigator contract. The abbreviated safety interim report written at the end of the Phase Ia for Schedules A and B in patients with solid tumours together with the results of primary endpoint in Schedule C in patients with solid tumours may be the basis for a publication. However, concerning all the trial results including the Phase Ib results, they may not be published prior to finalization of the Clinical Trial Report.
The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF (Investigator Site File)."

8.1 TRIAL APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB / IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the trial, written informed consent must be obtained from each patient or from the patient's parents (both or one, based on national regulation) or from the legal guardian if the patient is not legally adult according to ICH / GCP and to the regulatory and legal requirements of the participating country. For a minor patient, in addition to the parents or legal guardian informed consent, the minor patient must also sign an informed assent. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the Investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.
For patients < legal age to be adult: If only mother or father (or one legal guardian) has sole legal custody, this needs to be confirmed with signature and date on the informed consent by the person with legal custody. Both documents (consent and assent) outline the participant's rights to decline to participate or to withdraw from the study at any time. Consenting/assenting

is a dynamic and continuous process that should be maintained during the trial. At each new treatment course the site staff should briefly discuss with legal representative for a minor patient and with the patient him/herself the main aspects of the trial, focusing in particular on any new information that might affect their willingness to continue the participation in the trial. The site staff is recommended to document this process in the medical records.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the Sponsor, Sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the Investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

eCRF for individual patients will be provided by the Sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.

For the eCRF, all data need to be derived from source documents, e.g.:

- Patient identification (gender, date of birth)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date (mandatory), and end date (if available))
- SAEs (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results (in validated electronic format, if available)
- Originals or copies of imaging diagnostics
- ECG results (original or copies of printouts)
- Completion of Patient's Participation in the trial
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g., medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

Technical information collected on PK sampling days (such as i.e. PK sampling times, weight of containers for urine PK, repeated vital signs linked with PK) may be collected on specific paper PK logs which will be considered as source data for related entries in eCRF and are considered part of the ISF.

8.3.2 Direct access to source data and documents

The Investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRF and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the Sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The CRA / on site monitor and auditor may review all eCRF, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular AE is "listed", i.e. is a known adverse reaction of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For BI 894999, this is the current version of the Investigator's Brochure (c03016865-02).
The current version of this reference document is provided in the ISF. No AEs are classified as listed for trial design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IRB / IEC

Expedited reporting of SAEs, e.g. suspected unexpected serious adverse reactions (SUSAR) to health authorities and IRB / IEC, will be done according to local regulatory requirements. BI is responsible to fulfil their legal regulatory reporting obligations and in accordance to the requirements defined in this protocol.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.
Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the Sponsor's representatives, by the IEC and the regulatory authorities.

8.6 END OF TRIAL

The end of the trial is defined as the time when the last ongoing patient in the trial will have undergone the EOT visit and the EOR visit.

The IRB / IEC / competent authority in each participating EU member state needs to be notified about the end of the trial or early termination of the trial.

The last patient last visit primary endpoint (LPLV PE) is defined as the date when the last patient with solid tumour of the dose escalation Phase Ia from Schedules A and B has reached the end of 21 days in Cycle 1 and is evaluable for DLTs.

Overall survival status collection for NC patients will end 12 months after the end of trial.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P12-05791 U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for industry: drug interaction studies - study design, data analysis, implications for dosing, and labeling recommendations (draft guidance, February 2012) (this guidance document is being distributed for comment purposes only)). Website:fda.gov/downloads/Drugs/ GuidanceComplianceRegulatoryInformation/Guida nces/ucm292362.pdf (access date: 14 May 2012) ; U.S.Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) 2012.

P14-08681 European Medicines Agency (EMA). Committee for Human Medicinal Products (CHMP): guideline on the investigation of drug interactions, final (21 June 2012, CPMP/EWP/560/95/Rev. 1 Corr.) (this guideline replaces guideline CPMP/EWP/560/95). Website: ema.europa.eu/docs/en GB/ document_library/Scientific_guideline/2012/0 7/WC500129606.pdf (access date: 4 June 2014) ; London: European Medicines Agency (EMA) 2012.

R01-0787 Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

R04-0569 Kang SH, Ahn CW. An investigation of the traditional algorithm-based designs for phase 1 cancer clinical trials. Drug Inf J 2002. 36:865-873.

R06-0986 Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. Ann Oncol 2006; 17(1): 20-28.

R09-0262 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-247.

R10-4848 Common terminology criteria for adverse events (CTCAE) Version 4.0 published: May 28, 2009 (v4.03: June 14, 2010). Website: evs.nci.nih.gov/ftp1/ctcae_4.03.2010-06-14_quickreference_8.5x11.pdf

R13-4802 Jaki T, Clive S, Weir CJ. Principles of dose finding studies in cancer: a comparison of trial designs. Cancer Chemother Pharmacol 2013. 71:1107-1114.

R13-4803 Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med 2008. 27:2420-2439.

R13-4804 Rogatko A, Schoeneck D, Jonas W, Tighiouart M, Khuri FR, Porter A. Translation of innovative designs into phase I trials. J Clin Oncol 2007. 25(31):4982-4986.

R13-4805 Tourneau C le, Gan HK, Razak ARA, Paoletti X. Efficiency of new dose escalation designs in dose-finding phase I trials of molecularly targeted agents. Plos One 2012. 7(12):e51039.

R13-4806 Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. Stat Med 1998. 17:1103-1120.

R14-3387 Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 32, (2014).

R15-1329 Stathis A, et al. Results of a first-in-man phase I trial assessing OTX015, an orally available BET-bromodomain (BRD) inhibitor, in advanced hematologic malignancies. EORTC-NCI-AACR Annual Meeting, 2014. Abstract 5LBA.

R15-4233 Zhao W, Yang H, editors. Statistical methods in drug combination studies. (CRC Biostatistics Series) Boca Raton: CRC Press (2015)

R16-1012 Abramson J, et al. BET Inhibitor CPI-0610 is well tolerated and induces responses in Diffuse Large B-Cell Lymphoma and Follicular Lymphoma: preliminary analysis of an ongoing Phase 1 study. Blood 2015; 126 (23):1491.

R16-1148 NCCN clinical practice guidelines in oncology (NCCN Guidelines): non-Hodgkin's lymphomas (version 2.2016). http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (access date: 14 March 2016) ; National Comprehensive Cancer Network (NCCN) 2016.

R16-5269 Nagueh SF, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016; 29: 277-314.

R17-3376 Barrington SF, et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. Eur J Nucl Med Mol Imaging (2010) 37:1824–1833

R17-3377 Scher HI, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol 34: 1402-1418, 2016.

R17-3378 Younes A, et al. International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). Annals of Oncology 28: 1436-1447, 2017.

R17-3435 Neuenschwander B, et al. Robust exchangeability designs for early phase clinical trials with multiple strata. Pharmaceut. Statis. 2015, 15 123-134

R18-1831 Forero-Torres A, et al. Preliminary results from an ongoing Phase1/2 study of INCB057643, a bromodomain and extraterminal protein inhibitor, in patients with advanced malignancies. ASH17 BET 57643 poster_KL20_FINAL.pdf

R18-2390 Dawson MA, Stein E, Huntley B, et al. A Phase I Study of GSK525762, a selective bromodomain (BRD) and extra-terminal protein (BET) inhibitor: results of part 1 of Phase I/II open-label single-agent study in patients with acute myeloid leukemia (AML). 59th Conference of the American Society of Hematology (ASH), Atlanta, 9 - 12 Dec 2017 (Poster) 2017.

R18-2451 Giridhar P, et al. Patterns of care and impact of prognostic factors in the outcome of NUT midline carcinoma: a systematic review and individual patient data analysis of 119 cases. European Archives of Oto-Rhino-Laryngology (2018) 275:815–821

R19-0148 Meille C, et al. PKPD modeling of preclinical anti-tumor activity translates to first-in-human phase I study of MDM2 inhibitor HDM201. Annual Meeting of the Population Approach Group in Europe, 2018, Abstract 8633

9.2 UNPUBLISHED REFERENCES

c03016865-02 [redacted] Investigator's Brochure: BI 894999. Project 1367.P1, Version 2, 6 April 2016.

n00240842-01 [redacted], Investigations on the in vitro metabolism of [14C]BI 894999 and assessment of the human cytochrome P450 enzymes that are involved.

n00240650-01 [redacted], Prediction of BI 894999 Pharmacokinetics and Therapeutic Dose in human.

n00241936 [redacted] Effects of the BRD4 (BET) inhibitor BI 894999 on the proliferation of human lymphoma cell lines. 08 Apr 2015.

n00244406 [redacted] BI 894999: In vitro cytochrome P450 enzyme induction in primary human hepatocytes.

10. APPENDICES

10.1 PHARMACOKINETIC ANALYSES

Concentrations will be used for calculations in the format that is reported in the bio-analytical report. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. For the calculation of pharmacokinetic parameters, only concentrations within the validated concentration range will be used. The actual sampling times will be used. For pre-dose samples, the actual sampling time will be set to zero. Non-compartmental pharmacokinetic parameters will be determined using WinNonlin or another validated program.

Analyte plasma concentrations will be plotted graphically versus time for all subjects as listed in the analyte plasma concentration-time tables. For the presentation of the mean profiles, the arithmetic/geometric mean and the planned blood sampling times will be used.
In the following, the derivation of parameters that are determined after the first dose as single dose parameters and after the last dose of cycle 1as steady state parameters are described together, whereby (ss) denotes the steady state parameters. The derivation of parameters is not affected by the attainment of steady state.

C_{max} [redacted] Individual C_{max} [redacted] values will be directly determined from the plasma concentration time profiles of each subject. [redacted]

[redacted]

AUC: The area under the curve will be calculated using the linear up/log down algorithm. If an analyte concentration is equal to or higher than the preceding concentration, the linear trapezoidal method will be used. If the analyte concentration is smaller than the preceding concentration, the logarithmic method will be used.
Linear trapezoidal rule ($t_2 > t_1$ and $C_{t2} \geq C_{t1}$):
The area of the trapezoid between the two data points (t_1, C_{t1}) and (t_2, C_{t2}) will be computed by:

$$AUC_{t1\text{-}t2} = 0.5 \times (t_2 - t_1) \times (C_{t1} + C_{t2})$$

Logarithmic trapezoid rule ($t_2 > t_1$ and $C_{t2} < C_{t1}$):

The area of the trapezoid between the two data points (t_1, C_{t1}) and (t_2, C_{t2}) will be computed by:

$$AUC_{t1-t2} = \frac{(t_2 - t_1) \times (C_{t2} - C_{t1})}{\ln(C_{t2}/C_{t1})}$$

[redacted]

[redacted]

gMean, gCV: The geometric mean (gMean) and coefficient of variation, gCV (given in %), will be calculated by the formulae:

$$\text{gMean} = \exp\left[\frac{1}{n}\sum_{i=1}^{n}\ln(x_i)\right] = \exp\left[\overline{\ln(x_i)}\right]$$

$$\text{gCV}(\%) = 100 \cdot \sqrt{\exp\left[\text{Var}(\ln(x_i))\right] - 1}$$

where

$$\text{Var}(\ln(x_i)) = \frac{1}{n-1}\sum_{i=1}^{n}\left[\ln(x_i) - \overline{\ln(x_i)}\right]^2$$

10.2 TIME SCHEDULE FOR PHARMACOKINETIC (PK) AND BIOMARKER BLOOD SAMPLING

10.2.1 Blood and urine sampling schedule

Table 10.2.1: 1 Time schedule for PK blood and urine samplings and HEXIM1 biomarker blood sampling during treatment Cycle 1 in Schedule A (except for food interaction cohorts)

					Blood		**Urine**
Cycle	**Visit**	**Day**	**Time Point [hh:min]/event**	**CRF Time planned**	**Plasma for PK**	**Whole Blood for HEXIM1gene expression**	**Urine for PK**
1	1	1	Just before drug administration	-0:05	x	x	x
			BI 894999 administration	0:00			
			0:30	0:30	x		
			1:00	1:00	x		
			2:00	2:00	x	x	
			3:00	3:00	x		
			4:00	4:00	x	x	
			6:00	6:00	x		
			8:00	8:00	x	x	
		2	Just before drug administration	23:55	x	x	
			BI 894999 administration	24:00			
	2	8	Just before drug administration	167:55	x		
			BI 894999 administration	168:00			
	3	12	Just before drug administration	263:55	x		
			BI 894999 administration	264:00			
	4	14	Just before drug administration	311:55	x	x	x
			BI 894999 administration	312:00			
			0:30	312:30	x		
			1:00	313:00	x		
			2:00	314:00	x	x	
			3:00	315:00	x		
			4:00	316:00	x	x	
			6:00	318:00	x		
			8:00	320:00	x	x	

Table 10.2.1: 1 Time schedule for PK blood and urine samplings and HEXIM1 biomarker blood sampling during treatment Cycle 1 in Schedule A (except for food interaction cohorts) (continued)

					Blood		**Urine**
Cycle	**Visit**	**Day**	**Time Point [hh:min]/event**	**CRF Time planned**	**Plasma for PK**	**Whole Blood for HEXIM1 gene expression**	**Urine for PK**
1	4	15	Just before drug administration	335:55	x	x	
			BI 894999 administration	336:00			

Table 10.2.1: 2 Time schedule for PK blood and urine samplings and HEXIM1 biomarker blood sampling during treatment Cycles 1-2 in Schedule B (except for food interaction cohorts)

					Blood		**Urine**
Cycle	**Visit**	**Day**	**Time Point [hh:min]/event**	**CRF Time planned**	**Plasma for PK**	**Whole Blood for HEXIM1 gene expression**	**Urine for PK**
1	1	1	Just before drug administration	-0:05	x	x	x
			BI 894999 administration	0:00			
			0:30	0:30	x		
			1:00	1:00	x		
			2:00	2:00	x	x	
			3:00	3:00	x		
			4:00	4:00	x	x	
			6:00	6:00	x		
			8:00	8:00	x	x	
		2	Just before drug administration	23:55	x	x	
			BI 894999 administration	24:00			
	2	8	Just before drug administration	167:55	x		
			BI 894999 administration	168:00			
	3	12	Just before drug administration	263:55	x		

Table 10.2.1: 2 Time schedule for PK blood and urine samplings and HEXIM1 biomarker blood sampling during treatment Cycles 1-2 in Schedule B (except for food interaction cohorts) (continued)

					Blood		**Urine**
Cycle	**Visit**	**Day**	**Time Point [hh:min]/event**	**CRF Time planned**	**Plasma for PK**	**Whole Blood for HEXIM1 gene expression**	**Urine for PK**
1	3	12	BI 894999 administration	264:00			
	4	14	Just before drug administration	311:55	x	x	x
			BI 894999 administration	312:00			
			0:30	312:30	x		
			1:00	313:00	x		
			2:00	314:00	x	x	
			3:00	315:00	x		
			4:00	316:00	x	x	
			6:00	318:00	x		
			8:00	320:00	x	x	
		15	24:00	336:00	x	x	
			26:00	338:00		x	
			28:00	340:00		x	
			32:00	344:00		x	
		18	At time of visit	408:00	x	x	
2	1	1	Just before drug administration	-0:05	x	x	
			BI 894999 administration	0:00			
			2:00	2:00	x	x	
			4:00	4:00	x	x	
			8:00	8:00	x	x	
		2	Just before drug administration	23:55	x	x	
			BI 894999 administration	24:00			

Table 10.2.1: 3 Time schedule for PK blood and urine samplings and HEXIM1 biomarker blood sampling during treatment Cycle 1 in Schedule C for patients with solid tumours in Phase Ia

					Blood		**Urine**
Cycle	**Visit**	**Day**	**Time Point [hh:min]/event**	**CRF Time planned**	**Plasma for PK**	**Whole Blood for HEXIM1 gene expression**	**Urine for PK***
1	1	1	Just before drug administration	-0:05	x	x	x
			BI 894999 administration	0:00			
			0:30	0:30	x		
			1:00	1:00	x		
			2:00	2:00	x	x	
			3:00	3:00	x		
			4:00	4:00	x	x	
			6:00	6:00	x		
			8:00	8:00	x	x	
		2	Just before drug administration	23:55	x	x	
			BI 894999 administration	24:00			
	2	8	At time of visit	168:00	x		
	4	21	Just before drug administration	479:55	x	x	x
			BI 894999 administration	480:00			
			0:30	480:30	x		
			1:00	481:00	x		
			2:00	482:00	x	x	
			3:00	483:00	x		
			4:00	484:00	x	x	
			6:00	486:00	x		
			8:00	488:00	x	x	
		22	24:00	504:00	x	x	
			26:00	506:00		x	
			28:00	508:00		x	
			32:00	512:00	x	x	
	5	29	At time of visit	672:00	x		

*starting from protocol version 12.0, no urine collection anymore for PK

Table 10.2.1: 4 Time schedule for PK blood samplings and HEXIM1 biomarker blood sampling during treatment Cycle 1 in Schedule C for DLBCL and NC patients starting from protocol version 12.0

					Blood	
Cycle	**Visit**	**Day**	**Time Point [hh:min]/event**	**CRF Time planned**	**Plasma for PK**	**Whole Blood for HEXIM1 gene expression**
1	1	1	Just before drug administration	-0:05	x	x
			BI 894999 administration	0:00		
			2:00	2:00	x	
			3:00	3:00	x	
			4:00	4:00	x	x
	4	21	Just before drug administration	479:55	x	x
			BI 894999 administration	480:00		
			0:30	480:30	x	
			1:00	481:00	x	
			2:00	482:00	x	
			3:00	483:00	x	
			4:00	484:00	x	x
			6:00	486:00	x	
			8:00	488:00	x	
		22	24:00	504:00	x	x
	5	29	At time of visit	672:00	x	

10.2.2 Details of procedures for food interaction cohorts

[redacted]

Table 10.2.2: 1 Time schedule for PK blood and urine samplings and HEXIM1 biomarker blood sampling during treatment Cycle 1 in Schedule A (for food interaction cohorts)

					Blood		Urine
Cycle	**Visit**	**Day**	**Time Point [hh:min]/event**	**CRF Time planned**	**Plasma for PK**	**Whole Blood for HEXIM1gene expression**	**Urine for PK**
1	1	1	-0:30: Breakfast[1]	-0:30			
			Just before drug administration	-0:05	x	x	x
			BI 894999 administration	0:00			
			0:30	0:30	x		
			1:00	1:00	x		
			2:00	2:00	x	x	
			2:05: Snack[2]	2:05			
			3:00	3:00	x		
			4:00	4:00	x	x	
			6:00	6:00	x		
			8:00	8:00	x	x	
		2	23:30: Breakfast[2]	23:30			
			Just before drug administration	23:55	x	x	
			BI 894999 administration	24:00			
			0:30	24:30	x		
			1:00	25:00	x		
			2:00	26:00	x		
			2:05: Snack[2]	26:05			
			3:00	27:00	x		
			4:00	28:00	x		
			~~4:05: Snack[2]~~	~~28:05~~			
			6:00	30:00	x		
			8:00	32:00	x		
		3	Just before drug administration	47:55	x		
			BI 894999 administration	48:00			
	2	8	Just before drug administration	167:55	x		
			BI 894999 administration	168:00			
	3	12	Just before drug administration	263:55	x		
			BI 894999 administration	264:00			

Table 10.2.2: 1 Time schedule for PK blood and urine samplings and HEXIM1 biomarker blood sampling during treatment Cycle 1 in Schedule A (for food interaction cohorts) (continued)

					Blood		Urine
Cycle	**Visit**	**Day**	**Time Point [hh:min]/event**	**CRF Time planned**	**Plasma for PK**	**Whole Blood for HEXIM1gene expression**	**Urine for PK**
1	4	14	Just before drug administration	311:55	x	x	x
			BI 894999 administration	312:00			
			0:30	312:30	x		
			1:00	313:00	x		
			2:00	314:00	x	x	
			3:00	315:00	x		
			4:00	316:00	x	x	
			6:00	318:00	x		
			8:00	320:00	x	x	
		15	Just before drug administration	335:55	x	x	
			BI 894999 administration	336:00			

1 Only for patients who are under fasted conditions on Day 2 of Visit 1
2 Only for patients who are under fasted conditions on Day 1 of Visit 1, snack or meal after at least 2 hours fasted after intake of study medication

Table 10.2.2: 2 Time schedule for PK blood and urine samplings and HEXIM1 biomarker blood sampling during treatment Cycles 1-2 in Schedule B (for food interaction cohorts)

					Blood		Urine
Cycle	**Visit**	**Day**	**Time Point [hh:min]/event**	**CRF Time planned**	**Plasma for PK**	**Whole Blood for HEXIM1 gene expression**	**Urine for PK**
1	1	1	-0:30: Breakfast[1]	-0:30			
			Just before drug administration	-0:05	x	x	x
			BI 894999 administration	0:00			
			0:30	0:30	x		
			1:00	1:00	x		
			2:00	2:00	x	x	
			2:05: Snack[2]	2:05			
			3:00	3:00	x		

Table 10.2.2: 2 Time schedule for PK blood and urine samplings and HEXIM1 biomarker blood sampling during treatment Cycles 1-2 in Schedule B (for food interaction cohorts) (continued)

					Blood		**Urine**
Cycle	**Visit**	**Day**	**Time Point [hh:min]/event**	**CRF Time planned**	**Plasma for PK**	**Whole Blood for HEXIM1 gene expression**	**Urine for PK**
1	1	1	4:00	4:00	x	x	
			6:00	6:00	x		
			8:00	8:00	x	x	
		2	23:30: Breakfast[2]	23:30			
			Just before drug administration	23:55	x	x	
			BI 894999 administration	24:00			
			0:30	24:30	x		
			1:00	25:00	x		
			2:00	26:00	x		
			2:05: Snack[2]	26:05			
			3:00	27:00	x		
			4:00	28:00	x		
			6:00	30:00	x		
			8:00	32:00	x		
		3	Just before drug administration	47:55	x		
			BI 894999 administration	48:00			
	2	8	Just before drug administration	167:55	x		
			BI 894999 administration	168:00			
	3	12	Just before drug administration	263:55	x		
			BI 894999 administration	264:00			
	4	14	Just before drug administration	311:55	x	x	x
			BI 894999 administration	312:00			
			0:30	312:30	x		
			1:00	313:00	x		
			2:00	314:00	x	x	
			3:00	315:00	x		
			4:00	316:00	x	x	
			6:00	318:00	x		
			8:00	320:00	x	x	
		15	24:00	336:00	x	x	

Table 10.2.2: 2 Time schedule for PK blood and urine samplings and gene expression biomarker blood sampling during treatment Cycles 1-2 in Schedule B (for food interaction cohorts) (continued)

					Blood		**Urine**
Cycle	**Visit**	**Day**	**Time Point [hh:min]/event**	**CRF Time planned**	**Plasma for PK**	**Whole Blood for HEXIM1 gene expression**	**Urine for PK**
1	4	15	26:00	338:00		x	
			28:00	340:00		x	
			32:00	344:00		x	
		18	At time of visit	408:00	x	x	
2	1	1	Just before drug administration	-0:05	x	x	
			BI 894999 administration	0:00			
			2:00	2:00	x	x	
			4:00	4:00	x	x	
			8:00	8:00	x	x	
		2	Just before drug administration	23:55	x	x	
			BI 894999 administration	24:00			

1 Only for patients who are under fasted conditions on Day 2 of Visit 1
2 Only for patients who are under fasted conditions on Day 1 of Visit 1. Snack or meal after at least 2 hours fasted after intake of study medication

10.3 STATISTICAL APPENDIX INCLUDING MODEL PERFORMANCE AND DATA SCENARIOS

10.3.1 Model Performance and Data Scenarios for Schedules A and B

The model was assessed by two different metrics: hypothetical on-study data scenarios and long-run operating characteristics. The simulations for scenarios and operating characteristics were produced using R version 3.0.3.

Hypothetical data scenarios

Hypothetical data scenarios are shown in Table 10.3.1:1. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model. For each scenario, the probability of overdose for the current dose, the next optimal dose recommended by the model in terms of the probability of target dose, and the next maximal dose allowed by the model due to the bound of the overdose probability are shown. Furthermore the related probabilities of under-dosing, target dose, and overdosing for the next optimal dose are presented. The actual dose chosen for the next cohort, not shown in Table 10.3.1: 1, will be determined by the DMC after taking into consideration of the recommended dose from the model as well as other relevant data from this study.

For example, scenario 1 represents the case that no DLT is observed in the first patient at the starting dose of 0.2 mg. In this case, the next optimal dose, i.e. the dose with the highest probability of being in the target interval, is 40 mg. However since this dose has an overdose probability higher than 0.25, the next dose maximally allowed by the model is 20 mg. Similarly scenarios 2, 3, 5, 8, 9, 11, 12, 13 and 16 represent cases where no DLTs are observed. In scenario 4, one DLT is observed already in the patient at the second lowest dose level. There, the model recommends stopping the trial, because all pre-specified dose levels have high overdose probabilities. The same holds for scenario 7.

Finally, scenarios 14, 15, 17, and 19 illustrate cases where no DLTs are observed in the first patient cohorts and then DLTs occur in the higher dose levels. In scenarios 14 and 15, the model requires to re-enrol at 40 mg and at 80 mg, respectively. In both scenarios 17 and 19, 2 DLTs occur which lead to a direct reaction of the model despite the fact that no DLTs were seen in the previous cohorts. It therefore recommends de-escalating to lower dose levels. These cases illustrate the adaptive behaviour of the model even in extreme situations.

Table 10.3.1: 1 Hypothetical data scenarios

Scenario	Dose (mg)	# DLT	# Pat	Current Dose: P(OD)	Next optimal dose	Maximum dose allowed	Next optimal dose		
							P(UD)	P(TD)	P(OD)
1	0.2	0	[redacted]	0.047	40	20	0.446	0.182	**0.372****
2	0.2 0.5	0* 0		0.035	80	20	0.324	0.190	**0.486****

Table 10.3.1: 1 Hypothetical data scenarios (continued)

Scenario	Dose (mg)	# DLT	# Pat	Current Dose: P(OD)	Next optimal dose	Maximum dose allowed	Next optimal dose		
							P(UD)	P(TD)	P(OD)
3	0.2 1.0	0 0	[redacted]	0.034	80	20	0.333	0.196	**0.470****
4	0.2 0.5	0* 1		0.487	0.2	NA	0.352	0.249	**0.399****
5	0.2 1.0	0 0		0.015	80	20	0.362	0.201	**0.436****
6	0.2 1.0	0 1		0.248	2.5	1.0	0.315	0.313	**0.372****
7	0.2 1.0	0 2		0.645	0.2	NA	0.265	0.325	**0.410****
8	0.2 1.0 2.5	0 0 0		0.007	80	40	0.406	0.204	**0.389****
9	0.2 1.0 5.0	0 0 0		0.056	80	20	0.368	0.200	**0.432****
10	0.2 1.0 5.0	0 0 1		0.241	10	5.0	0.304	0.320	**0.375****
11	0.2 1.0 2.5 5.0	0 0 0 0		0.004	80	40	0.446	0.195	**0.360****
12	0.2 1.0 5.0 10	0 0 0 0		0.018	80	40	0.446	0.213	**0.340****

Table 10.3.1: 1 Hypothetical data scenarios (continued)

Scenario	Dose (mg)	# DLT	# Pat	Current Dose: P(OD)	Next optimal dose	Maximum dose allowed	Next optimal dose		
							P(UD)	P(TD)	P(OD)
13	0.2 1.0 5.0 10 20	0 0 0 0 0	[redacted]	0.012	80	40	0.529	0.206	**0.265****
14	0.2 1.0 5.0 10 20 40	0 0 0 0 0 1	[redacted]	0.148	40	40	0.516	0.336	0.148
15	0.2 1.0 5.0 10 20 40 80	0 0 0 0 0 0 1	[redacted]	0.244	80	80	0.409	0.347	0.244
16	0.2 1.0 5.0 10 20 40 80	0 0 0 0 0 0 0	[redacted]	0.032	120	120	0.685	0.187	0.128
17	0.2 1.0 5.0 10 20 40 80	0 0 0 0 0 1 1	[redacted]	0.448	40	40	0.493	0.412	0.095

Table 10.3.1: 1 Hypothetical data scenarios (continued)

Scenario	Dose (mg)	# DLT	# Pat	Current Dose: P(OD)	Next optimal dose	Maximum dose allowed	Next optimal dose		
							P(UD)	P(TD)	P(OD)
18	0.2 1.0 5.0 10 20 40 80	0 0 0 0 0 1 0	[redacted]	0.149	80	80	0.506	0.345	0.149
19	0.2 1.0 5.0 10 20 40 80 120	0 0 0 0 0 0 0 2	[redacted]	0.582	80	80	0.399	0.428	0.173

*non-DLT drug-related AE of CTCAE grade >=2
****Overdose-probability of the next optimal dose is too high (violates EWOC criterion), therefore the maximal allowed dose would be chosen as next dose by the model.**

Operating characteristics

Operating characteristics are a way to assess the long-run behaviour of a model. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulation. Table 10.3.1: 2 describes 5 assumed true dose-toxicity scenarios which were used to assess the operating characteristics of the model. These scenarios reflect a wide range of possible cases. Scenario 1 represents the DLT rates that are aligned with prior means per dose level. Scenarios 2 and 3 reflect the extreme cases of very high and very low toxicity probabilities, respectively. Scenario 4 covers the case of a true dose-toxicity relationship that does not have a logistic form. Finally, scenario 5 reflects the possibility of having very low DLT rates at the lower dose levels and high DLT rates at the upper dose levels.

Table 10.3.1: 2 Assumed true dose-toxicity scenarios

Scena -rio	Dose (mg)									
	0.2	0.5	1.0	2.5	5.0	10	20	40	80	120
1: Prior	0.102	0.119	0.136	**0.164**	**0.191**	**0.226**	**0.273**	0.339	0.435	0.499
2: High Tox	0.100	**0.199**	**0.305**	**0.314**	0.387	0.456	0.498	0.527	0.600	0.723
3: Low Tox	0.001	0.005	0.009	0.013	0.028	0.041	0.050	0.057	0.060	**0.160**
4: Non-Logis-tic	0.020	0.050	0.065	0.080	0.130	**0.210**	**0.280**	**0.320**	0.380	0.410
5: Low-High	0.001	0.005	0.009	0.013	**0.314**	0.387	0.456	0.498	0.527	0.600

Bold numbers indicate true DLT rates in the target interval [0.16, 0.33].

For each of these scenarios, 1000 trials were simulated. It was then assessed how often a dose was declared as MTD with true DLT rate in the under-, targeted or over-dose range. Furthermore, the average, minimum and maximum number of patients per trial and the average number of DLTs per trial are reported. Results are shown in Table 10.3.1: 3.

Table 10.3.1: 3 Simulated operating characteristics

Scenario	% of trials declaring an MTD with true DLT rate in				# Patients	# DLT
	underdose	target dose	overdose	STOPPED	Mean (Min-Max)	Mean (Min- Max)
1	8.5	54.5	4.6	32.4	17.25 (3-48)	2.99 (1-9)
2	2.6	47.9	11.3	38.2	13.96 (3-42)	3.40 (1-11)
3	38.2	61.4	0	0.4	33.59 (3-60)	1.68 (0-7)
4	23.1	67.4	3.1	6.4	24.70 (3-51)	3.49 (1-10)
5	10.5	52.7	25.3	11.5	20.14 (3-39)	4.92 (2-13)

In scenario 1, which reflects the case that the true dose-toxicity is aligned with prior means, 54.5% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range. However, the starting dose 0.2 mg already has a DLT rate of 0.102. This contributes to the high percentage (32.4%) of all simulated trials for which the trial is stopped since none of

the doses is considered tolerable anymore. This is similar for scenario 2, where the DLT rate at the starting dose is 0.1, which leads to a high percentage of prematurely stopped trials (38.2%). But for a high-toxicity scenario, this is an expected situation.

Scenario 3 (low-toxicity scenario) shows, that even with small toxicity rates the model declares MTDs with true DLT rate in the targeted interval in a high percentage of trials (61.4%). Nevertheless, more patients are needed in this scenario. Since none of the pre-defined dose levels has a true DLT rate in the overdose range, only very few trials are stopped prematurely.
In both scenarios 4 and 5, more than 50% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range.

The mean patient numbers range from 17.25 (scenario 1) to 33.59 (low-toxicity scenario) and the maximum number of patients in one trial was 60. Therefore the patient numbers are as expected and decrease when moving away from the low-toxicity scenario.

In summary, the considered data scenarios show a reasonable behaviour of the model and the operating characteristics demonstrate a good precision of MTD determination.

Since dose escalation for Schedule B is conducted after the dose escalation for Schedule A, the initial mixture prior used for Schedule A dose escalation will be updated using the observed safety data on Schedule A to derive a meta-analytic predictive (MAP) prior for the BLRM of Schedule B. Two MAP priors are derived with one using the observed DLT in each dose of Schedule A and the other one using the observed DLT and with the doses in Schedule A being increased by 1.5 times to derive a corresponding dose in Schedule B which gives the same total dose in each 21-day treatment cycle. These 2 MAP priors are used with equal weight in the updated mixture prior of the BLRM for Schedule B dose escalation in the assessment of new hypothetical data scenarios. The details of these simulation analyses will be provided in the minutes of the regular DMC meetings.

Observed data in both schedule dose escalations will be used to update the prior used in the BLRM for patients with DLBCL with the selected schedule.

10.3.2 Statistical Appendix for Schedule C

To determine the MTD for Schedule C in solid tumour, patients are entered sequentially into escalating dose cohorts. The dose escalation will be guided by a Bayesian 5-parameter logistic regression model with overdose control (R15-4233).
This logistic regression model is defined as follows. Let π_1, d_1 be the probability of having a DLT when giving dose d_1 of BI 894999 maintenance dose as monotherapy, and π_2, d_2 the probability of having a DLT when giving dose d_2 of the combination partner BI 894999 loading dose as monotherapy, respectively. A logistic regression is used to model the dose-toxicity relationship for each of these dosing approachs individually:

Maintenance dose: $\text{logit}(\pi_{1,d1}) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$
Loading dose: $\text{logit}(\pi_{2,d2}) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$

Here, the doses $d_1^* = 4$ mg and $d_2^* = 5$ mg represent the reference doses for maintenance dose and loading dose, respectively.

In order to account for a potential positive (higher toxicity than expected under independence) interaction between maintenance dose and loading dose, a dose-dependent interaction term $0<\eta<\infty$ is introduced in the model by the following definition: $\text{odds}(\pi_{12,d1,d2}) = \text{odds}(\pi^0_{12,d1,d2}) \exp(\eta\, d_1/d_1^*\, d_2/d_2^*)$
and $\pi_{12,d1,d2}$ is used in the likelihood
$r_{d1,d2} \sim \text{Binomial}(n_{d1,d2},\pi_{12,d1,d2})$
where $r_{d1,d2}$ denotes the random variable describing the observed number of DLTs in $n_{d1,d2}$ patients at the dose combination d_1, d_2.

Since a Bayesian approach is applied, prior distributions f for each of the parameter vectors $\theta_1=(\log(\alpha_1),\log(\beta_1))$, $\theta_2=(\log(\alpha_2),\log(\beta_2))$ and for the interaction term η need to be specified.

An informative prior is used for maintenance dose using historical information from schedule A and B with two transformation methods.
The prior distribution for θ_1 will be specified as a mixture of two bivariate normal distributions,
$f(\theta_1) = a_1 f_1(\theta_1) + a_2 f_2(\theta_1)$
with
a_i, i = 1, 2 the prior mixture weights ($a_1 + a_2 = 1$)
and
$f_i(\theta_1) = \text{MVN}(\mu_i, \Sigma_i)$
the multivariate normal distribution of the i-th component with mean vector μ_i and covariance matrix Σ_i, where

$$\Sigma_i = \begin{pmatrix} \sigma^2_{i,11} & \sigma_{i,11}\sigma_{i,22}\rho_i \\ \sigma_{i,11}\sigma_{i,22}\rho_i & \sigma^2_{i,22} \end{pmatrix}$$

Mixture prior distributions have the advantage that they allow for specification of different logistic dose-toxicity curves, therefore making the prior more robust.

A minimally informative prior is used for loading dose:
The prior distributions for θ_2 will be specified as mixtures of three multivariate normal distributions, i.e.
$a(\theta_2) = a_1 f_1(\theta_2) + a_2 f_2(\theta_2) + a_3 f_3(\theta_2)$
with
a_i, i = 1, 2, 3 the prior mixture weights ($a_1 + a_2 + a_3 = 1$)
and
$f_i(\theta_2) = \text{MVN}(\mu_i, \Sigma_i)$,
the multivariate normal distribution of the i-th component with mean vector μ_i and covariance matrix Σ_i, where

$$\Sigma_i = \begin{pmatrix} \sigma^2_{i,11} & \sigma_{i,11}\sigma_{i,22}\rho_i \\ \sigma_{i,11}\sigma_{i,22}\rho_i & \sigma^2_{i,22} \end{pmatrix}$$

Mixture prior distributions have the advantage that they allow for specification of different logistic dose-toxicity curves, therefore making the prior more robust.

A weakly informative lognormal prior distribution will be used for η.

The estimated probability $\pi_{12,d1,d2}$ of a DLT at each dose combination d_1, d_2 from the model will be summarized using the following intervals:
Under toxicity: [0.00, 0.16)
Targeted toxicity: [0.16, 0.33)
Overtoxicity: [0.33, 1.00]

The BLRM-recommended dose combination for the next cohort is the level with the highest posterior probability of the DLT rate falling in the target interval [0.16, 0.33) among the dose combinations fulfilling the EWOC principle. Per EWOC it should be unlikely (<25% posterior probability) that the DLT rate at the dose combination will exceed 0.33. However, the maximum allowable dose increment for the subsequent cohort will be no more than 100% for each drug.

The MTD may be considered reached if one of the following criteria is fulfilled:
1. The posterior probability of the true DLT rate in the target interval [0.16 – 0.33) of the MTD is above 0.50, OR
2. At least 12 patients have been treated in the trial, of which at least 6 at the MTD.

Prior derivation:

To determine the maintenance dose prior distribution for θ_1 and θ_2, a meta-analytic predictive (MAP) approach will be used. Exact details on the derivation of the prior distributions and on the evaluation of the model using hypothetical data scenarios and operating characteristics are provided in the statistical appendix, a brief description is given here.

The following steps were used to derive the prior distributions for all parameters:

1. Maintenance dose θ_1:
   Toxicity information on schedule C from schedule A and B in Phase Ia will be incorporated in Table 10.3.2: 1 with two transformation methods separately, which are equal total dose transformation and equal daily dose transformation during MTD evaluation period. The meta-analytic-predictive prior was derived using the historical toxicity information, allowing for substantial between-trial heterogeneity.

2. Loading dose θ_2:
   (1) A low-toxicity weakly informative prior was derived reflecting the case that the compound would be much less toxic than expected. For this prior component, it was assumed that the median DLT rate at the starting dose of 2.5 mg would equal 0.001, and the median DLT rate at the anticipated MTD of 5 mg would equal 0.01. These assumptions yield $\mu_{31} = (-4.60, 1.20)$, i.e. basically a flat curve. The standard deviations and correlations were set to $\sigma_{31,11} = 2$, $\sigma_{31,22} = 1$, therefore almost fixing the slope parameter to its mean. The correlation was set to 0, i.e. $\rho_{31} = 0$. The prior weight $a_{3,1}$ for the third component was chosen as 0.8.

(2) A high-toxicity weakly informative prior was derived reflecting the case that the compound would be much more toxic than expected. For this prior component, it was assumed that the median DLT rate at the starting dose of 2.5 mg would equal 0.1, and the median DLT rate at the anticipated MTD of 5 mg would equal 0.2. These assumptions yield $\mu_{12} = (-1.39, 0.16)$. The standard deviations and correlations were set identical to the weakly informative prior, i.e. $\sigma_{21,11} = 2$, $\sigma_{21,22} = 1$ and $\rho_{21} = 0$, respectively. The prior weight $a_{2,1}$ for the second component was chosen as 0.1.

(3) A weakly informative prior was derived reflecting the a priori assumption that the median DLT rate at the starting dose of 2.5 mg would equal 0.01, and the median DLT rate at the anticipated MTD of 5 mg would equal 0.1. This yields $\mu_{11} = (-2.20, 1.24)$. The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{11,11} = 2$, $\sigma_{11,22} = 1$ and $\rho_{11} = 0$, respectively. The prior weight $a_{1,1}$ for the first component was chosen as 0.1.

3. Interaction term η:
Based on the a priori assumption of positive interaction between the two compounds, a lognormal distribution with mean -2.30 and standard deviation 1 was chosen. At the starting dose combination, the corresponding 95% prior interval covers an up to 4 fold increase (or decrease) in the odds of a DLT over positive interaction.

Table 10.3.2: 1 Historical data for BI 894999 of Schedule A and Schedule B

Schedule	Dose	N of patients with DLTs during MTD evaluation period / N of patients
Schedule A	0.2 mg	0/2
	0.5 mg	0/2
	1 mg	0/3
	1.5 mg	0/6
	2 mg	3/6
	5 mg	2/2
Schedule B	1.5 mg	1/5
	2 mg	0/6
	2.5 mg	2/13

A summary of the prior distributions is provided in Table 10.3.2: 2 and Table 10.3.2: 3. Additionally, the prior probabilities of DLTs at different dose combinations, as well as the corresponding probability of under-, targeted and overtoxicity, are shown in Table 10.3.2: 4. As can be seen from the tables, the prior medians of the DLT probabilities are in-line with the

prior medians derived from the weakly informative priors, and the uncertainty around the medians is large, showing the low amount of information these priors provide. This is also supported by the prior sample size, i.e. the information contained in the priors. This is approximately equal to 7.1 patients for the prior of the combination of loading dose and maintenance dose.

Table 10.3.2: 2 Prior distributions for loading dose

Prior Component	Mixture Weight	Mean Vector	SD Vector
Loading dose			
1: Weakly inf.	0.100	(-2.197, 1.241)	(2.000, 1.000)
2: High Tox.	0.100	(-1.386, 0.157)	(2.000, 1.000)
3: Low Tox.	0.800	(-4.595, 1.204)	(2.000, 1.000)

Table 10.3.2: 3 Prior distributions for maintenance dose

Parameter	means, standard deviations, correlation	mixture weight
$\log(\alpha_2)$, $\log(\beta_2)$: component 1	(-0.831, 1.045), (0.625, 0.611), 0.417	0.5
$\log(\alpha_2)$, $\log(\beta_2)$: component 2	(-0.066, 0.957), (0.846, 0.589), 0.680	0.5
η	-2.30, 1, N/A	N/A

Table 10.3.2: 4 Prior probabilities of DLTs at selected doses

Maintenance dose	Loading dose	Probability of true DLT rate in					Quantiles		
		[0,0.16)	**[0.16,0.33)**	**[0.33,1]**	**Mean**	**StD**	**2.5%**	**50%**	**97.5%**
2	1.5	0.75	0.204	0.046	0.12	0.113	0.004	0.092	0.409
2	2	0.733	0.214	0.053	0.126	0.12	0.004	0.095	0.444
2	2.5	0.717	0.222	0.061	0.132	0.126	0.005	0.099	0.476
2	3	0.7	0.229	0.071	0.139	0.133	0.006	0.103	0.515
2	3.5	0.679	0.239	0.083	0.146	0.141	0.007	0.108	0.56
2	4	0.654	0.249	0.098	0.156	0.149	0.008	0.114	0.607

Table 10.3.2: 4 Prior probabilities of DLTs at selected doses: continued

Maintenance dose	Loading dose	Probability of true DLT rate in					Quantiles		
		[0,0.16)	**[0.16,0.33)**	**[0.33,1]**	**Mean**	**StD**	**2.5%**	**50%**	**97.5%**
2	4.5	0.622	0.262	0.116	0.169	0.16	0.009	0.123	0.66
2	5	0.58	0.276	0.144	0.187	0.174	0.011	0.135	0.726
2	5.5	0.521	0.286	0.193	0.216	0.2	0.013	0.153	0.82
2	6	0.47	0.283	0.248	0.252	0.233	0.016	0.171	0.917
2.5	1.5	0.535	0.357	0.108	0.178	0.128	0.017	0.15	0.496
2.5	2	0.521	0.36	0.12	0.183	0.133	0.019	0.154	0.517
2.5	2.5	0.505	0.365	0.13	0.19	0.138	0.02	0.159	0.541
2.5	3	0.488	0.369	0.143	0.197	0.144	0.022	0.164	0.577
2.5	3.5	0.468	0.374	0.158	0.205	0.15	0.023	0.17	0.611
2.5	4	0.444	0.38	0.175	0.215	0.157	0.025	0.178	0.648
2.5	4.5	0.416	0.385	0.199	0.227	0.166	0.027	0.186	0.694
2.5	5	0.377	0.39	0.233	0.245	0.177	0.031	0.2	0.753
2.5	5.5	0.336	0.378	0.286	0.273	0.199	0.034	0.219	0.838
2.5	6	0.299	0.363	0.338	0.307	0.228	0.037	0.24	0.926
3	1.5	0.302	0.447	0.252	0.252	0.144	0.053	0.224	0.597
3	2	0.288	0.448	0.264	0.258	0.148	0.054	0.229	0.614
3	2.5	0.276	0.446	0.279	0.264	0.152	0.056	0.235	0.634
3	3	0.262	0.443	0.295	0.271	0.156	0.058	0.242	0.652
3	3.5	0.248	0.439	0.314	0.28	0.161	0.06	0.248	0.679
3	4	0.231	0.434	0.335	0.289	0.166	0.063	0.257	0.708
3	4.5	0.211	0.427	0.362	0.302	0.173	0.067	0.268	0.741
3	5	0.188	0.416	0.396	0.318	0.182	0.071	0.281	0.786
3	5.5	0.165	0.39	0.445	0.345	0.198	0.076	0.302	0.86
3	6	0.145	0.363	0.492	0.376	0.221	0.08	0.326	0.937
3.5	1.5	0.121	0.424	0.455	0.338	0.163	0.102	0.311	0.708
3.5	2	0.113	0.417	0.47	0.344	0.166	0.104	0.317	0.719
3.5	2.5	0.105	0.41	0.485	0.351	0.168	0.106	0.323	0.733
3.5	3	0.098	0.401	0.5	0.359	0.171	0.108	0.33	0.748
3.5	3.5	0.092	0.391	0.518	0.367	0.174	0.111	0.338	0.763
3.5	4	0.084	0.378	0.537	0.376	0.178	0.114	0.348	0.783

Table 10.3.2: 4 Prior probabilities of DLTs at selected doses: continued

Maintenance dose	Loading dose	Probability of true DLT rate in					Quantiles		
		[0,0.16)	**[0.16,0.33)**	**[0.33,1]**	**Mean**	**StD**	**2.5%**	**50%**	**97.5%**
3.5	4.5	0.075	0.364	0.561	0.388	0.182	0.118	0.36	0.806
3.5	5	0.065	0.343	0.591	0.404	0.188	0.123	0.376	0.836
3.5	5.5	0.055	0.315	0.63	0.428	0.199	0.128	0.398	0.885
3.5	6	0.048	0.285	0.668	0.456	0.215	0.133	0.423	0.947
4	1.5	0.045	0.306	0.649	0.427	0.184	0.138	0.404	0.82
4	2	0.041	0.297	0.662	0.434	0.185	0.14	0.412	0.827
4	2.5	0.038	0.288	0.674	0.44	0.187	0.143	0.419	0.835
4	3	0.035	0.277	0.688	0.448	0.188	0.146	0.427	0.844
4	3.5	0.032	0.265	0.703	0.456	0.19	0.149	0.436	0.851
4	4	0.03	0.252	0.718	0.465	0.192	0.153	0.446	0.862
4	4.5	0.027	0.237	0.736	0.476	0.194	0.157	0.458	0.874
4	5	0.023	0.22	0.757	0.49	0.197	0.165	0.473	0.889
4	5.5	0.018	0.197	0.784	0.511	0.203	0.172	0.496	0.92
4	6	0.016	0.178	0.806	0.536	0.213	0.18	0.521	0.96

Statistical model assessment

The model was assessed using hypothetical data scenarios and simulated operating characteristics. Hypothetical data scenarios are shown in Table 10.3.2: 5 reflecting potential on-study data constellations and related escalation as allowed by the model. Operating characteristics are assessed an assumed under assumed true dose-toxicity scenarios (Table 10.3.2: 6), and the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulation (Table 10.3.2: 7). More details are the same with model assessment for Schedule A and Schedule B which can be found in Section 10.3.1.

Table 10.3.2: 5 Hypothetical data scenarios

Scenario	Dose combination (loading/ maintenance: mg)	# Patients / # DLT	Current Dose combination: P(OD)	Next recommended dose combination	Next optimal dose		
					P(UD)	P(TD)	P(OD)
1	5.0 / 2.5	[redacted] / 0	0.057	6.0 / 3.0	0.342	0.466	0.192

Table 10.3.2: 5 Hypothetical data scenarios: continued

Scenario	Dose combination (loading/ maintenance: mg)	# Patients / # DLT	Current Dose combination: P(OD)	Next recommended dose combination	Next optimal dose		
					P(UD)	P(TD)	P(OD)
2	5.0 / 2.5 6.0 / 3.0	[redacted] 0 1	0.223	6.0 / 3.0	0.244	0.534	0.223
3	5.0 / 2.5 6.0 / 3.0 6.0 / 3.0	[redacted] 0 1 1	0.249	6.0 / 3.0	0.178	0.573	0.249
4	5.0 / 2.5 6.0 / 3.0	[redacted] 0 2	0.453	5.0 / 2.5	0.313	0.522	0.164
5	5.0 / 2.5	[redacted] 1	0.159	5.0 / 2.5	0.357	0.484	0.159
6	5.0 / 2.5 5.0 / 2.5	[redacted] 1 0	0.067	6 / 3	0.211	0.542	0.247
7	5.0 / 2.5 5.0 / 2.5 6.0 / 3.0	[redacted] 1 0 1	0.256	5.0 / 2.5	0.450	0.487	0.063
8	5.0 / 2.5 5.0 / 2.5	[redacted] 1 1	0.178	5.0 / 2.5	0.263	0.559	0.178

Table 10.3.2: 6 Assumed true dose-toxicity scenarios

Scena-rio	Loading dose (mg)/Maintenance dose (mg)								
	4.0/2.0	5.0/2.0	6.0/2.0	4.0/2.5	5.0/2.5	6.0/2.5	4.0/3.0	5.0/3.0	6.0/3.0
1: Prior	0.126	0.183	0.258	0.132	0.19	0.264	0.139	0.197	0.271
2: High Tox	0.24	0.27	0.31	0.265	0.29	0.33	0.289	0.33	0.36
3: Low Tox	0.007	0.013	0.017	0.012	0.016	0.020	0.015	0.019	0.160
4: Non-Logis-tic	0.05	0.065	0.085	0.064	0.09	0.11	0.082	0.12	0.160
5: Low-High	0.007	0.013	0.017	0.25	0.28	0.32	0.27	0.30	0.34

Table 10.3.2: 7 Simulated operating characteristics

Scenario	% of trials declaring an MTD with true DLT rate in				# Patients	# DLT
	underdose	target dose	overdose	STOPPED	Mean (Min-Max)	Mean (Min- Max)
1	3.4	74.3	0	17.4	14.53 (3-18)	3.19 (0-8)
2	0	20.7	40.9	16.9	12.90 (3-18)	3.84 (1-9)
3	0.9	86.1	0	13	14.06 (12-18)	1.29 (0-5)
4	4.8	82.6	0	12.1	14.19 (3-18)	1.66 (0-7)
5	0	9.2	70.1	20.7	14.70 (12-18)	2.83 (0-8)

10.4 VISIT SCHEDULE

10.4.1 For Cycle 1

Schedule A
- Visit 1 is Day 1 of first intake of BI 894999 and Day 2 (Day 3 in addition if in the food effect cohort)
- Visit 2 must be performed on day 8 plus or minus one day
- Visit 3 must be performed on day 12 plus or minus one day
- Visit 4 must be performed on Days 14 and 15
- Visit 5 must be performed on Day 22, corresponding to Day 1 of the new cycle (if no delay in further cycle).

Schedule B
- Visit 1 is Day 1 of first intake of BI 894999 and Day 2 (Day 3 in addition if in the [redacted] cohort)
- Visit 2 must be performed on day 8 plus or minus one day
- Visit 3 must be performed on day 12 plus or minus one day
- Visit 4 must be performed on Days 14 and 15 and on Day 18 plus or minus one day
- Visit 5 must be performed on Day 22, corresponding to Day 1 of the new cycle (if no delay in further cycle)

Schedule C
- Visit 1 is Day 1 of first intake of BI 894999 (loading dose) and Day 2 (maintenance dose) (only Day 1 for DLBCL and NC patients after approval of protocol version 12.0)
- Visit 2 must be performed on Day 8
- Visit 3 must be performed on Day 15 with second loading dose intake of the cycle
- Visit 4 must be performed on Days 21 and 22
- Visit 5 must be performed on Day 29, corresponding to Day 1 of the new cycle (if no delay in further cycle)

10.4.2 For Cycle 2

Schedule A
- Visit 1 is on the first day of intake of BI 894999 of the second cycle (which may correspond to last visit of first cycle)
- Visit 2 will take place on Day 15 (- 4 + 2)
- Visit 3 must be performed on Day 22, which may correspond to Day 1 of third cycle

Schedule B
- Visit 1 is on the first day of intake of BI 894999 of the second cycle (which may correspond to last visit of first cycle) and on the second day
- Visit 2 will take place on Day 15 (-4 + 2)
- Visit 3 must be performed on Day 22, which may correspond to Day 1 of third cycle

Schedule C

- Visit 1 is on the first day of intake of BI 894999 (loading dose) of the second cycle (which may correspond to last visit of first cycle)
- Visit 2 will take place on Day 15 for second loading dose of the cycle
- Visit 3 must be performed on Day 29, which may correspond to Day 1 of third cycle

10.4.3 For next cycles in all Schedules

- Visit 1 is the first day of intake of BI 894999 of the next cycle and may correspond to last visit of previous cycle with returns on Day 15 (-4 +2 for Schedules A and B, no window allowed for Schedule C) for safety blood sampling and ECG. This visit may become optional starting from Cycle 5 onwards for Schedules A and B if there are no cardiac safety concerns as judged by the investigator from previous results. The visit will remain mandatory for all cycles in Schedule C
- Visit 2 must be performed on Day 22 for Schedules A and B, on Day 29 for Schedule C, which may correspond to Day 1 of any new cycle.

Once the decision for any reason is taken for a patient to stop the treatment with BI 894999, an EOT visit must occur as soon as possible.
After the EOT visit, the patient must undergo a follow-up evaluation during a visit (or at least a phone contact if a visit is not possible), 30 days (+7) days after the last BI 894999 intake.
If the patient was not discontinued because of withdrawal of consent, disease progression or treatment with another anti-cancer drug, he/she must continue to undergo follow-up visits every 12 weeks until progression, lost to follow-up, treatment with another anti-cancer therapy or the end of the trial.

10.5 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

10.5.1 Screening period for all Schedules

The screening period may run over a period of 28 days (period within the trial and before the very first intake of BI 894999) and will include the following:

- Informed consents
- Demographics (sex, birth date (year)), race, ethnicity, alcohol and smoking history)
- Medical history (oncologic history and any relevant non-oncologic history)
- Occurrence of AEs since signature of the informed consent form
- Concomitant therapy
- Physical examination including body weight, height, vital signs and ECOG performance score. The physical examination will also include a tumour evaluation by palpation for the DLBCL patients
- Resting 12-lead ECG
- LVEF by MUGA scan or echocardiography
- Safety laboratory parameters, including haematology with differential, biochemistry including troponin hs, coagulation parameters, tumour markers if applicable (PSA mandatory for mCRPC patients), virology for Hep B, Hep C and HIV (from protocol version 9 onwards) and urinalysis
- β-HCG serum or urine pregnancy test for women of childbearing potential (within 7 days before first treatment intake)
- Baseline tumour assessment
  - with CT scan or MRI (if not performed within previous 6 weeks) in solid tumours including mCRPC patients
  - with FDG-PET/CT (or MRI) scan for DLBCL patients (if not performed within previous 6 weeks
  - bone scan for mCRPC patients in Phase Ib (if not performed within previous 6 weeks)
- Baseline tumour biopsy optional, for patients in the escalation part until MTD and for patients in the MTD extension cohort and mandatory for patients in the expansion Phase Ib (not requested for mCRPC patients presenting only with bone metastases or for patients with therapeutic INR because of treatment with a vitamin K antagonist or a novel oral anticoagulant, optional for NC patients) (platelet count and coagulation must be checked prior to each biopsy and must be adequate) (see 3.3.2 and 5.5). If archival tumour tissue sampled within 6 months of inclusion in this trial is available, archival tumour tissue may be used instead of a fresh biopsy
- Mandatory 2-3 mL EDTA blood DNA sample for the patients who undergo a tumour biopsy or for whom archival tumour tissue is sent (sample to be collected only once during the trial, at any time)
- Patient's eligibility (inclusion and exclusion criteria)

10.5.2 Treatment period

10.5.2.1 Cycle 1

Visit 1 on Day 1 for all Schedules

- Review of patient's eligibility
- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Physical examination including body weight and ECOG performance score
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position before the study drug intake and then according to the time points as specified in the Flow Chart
- Digitalised 12-lead ECGs if possible in triplicate taken after at least 5 min rest in supine position before intake of BI 894999 and then at several time points (see 5.3.4 and Flow Chart)
- Safety laboratory parameters if previous lab older than 72 hours, including haematology with differential, biochemistry (with CK and troponin hs) and coagulation parameters (plus factors II, V, VII and IX in 20 first patients of Phase Ib), and urinalysis via dipstick to confirm eligibility prior to trial drug intake
- Plasma and urine PK samplings (see 5.4, Flow Chart and Appendix 10.2). No urine PK samplings from protocol version 12.0 onwards
- Whole blood sampling for HEXIM1 (or other genes related to the MOA of BI 894999) gene expression before intake of BI 894999 and then at several time points (see 5.5, Appendix 10.2 and Flow Chart)
- Optional blood sampling for DNA bio-banking (separate informed consent)

Whenever vital signs, digitalized ECGs and PK sampling must happen at the same time-point, vital signs will be taken first, then ECGs (which should be taken after 5 minutes resting after the vital signs are taken) and only afterwards, the PK samplings.

- Breakfast a half hour before first dosing for the food interaction cohort only, for patients who are under fasted conditions on Day 2 of Visit 1 (see Appendix 10.2.2)
- First oral intake of BI 894999 (loading dose in Schedule C)
- Completion of a diary card indicating the intake of BI 894999 with date and hour.
- Snack at least 2h post-dose for the food interaction cohort only, for patients who are under fasted conditions on Day 1 of Visit 1 (see Appendix 10.2.2)

Visit 1 on Day 2 for all Schedules (no visit anymore on Day 2 for NC and DLBCL patients in Schedule C, starting from protocol version 12.0)

- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position before the second study drug intake as specified in the flow chart. See also Appendix 10.2 for the timing of PK samplings to be performed during PK days (see 5.4 and Flow Chart)
- Digitalised, if possible triplicate, 12-lead ECGs taken after at least 5 min rest in supine position 24h after first dose intake and just before second intake of BI 894999 (see 5.3.4 and Flow Chart)
- Safety laboratory parameters, including haematology with differential, biochemistry including troponin hs and coagulation parameters, and urinalysis by dipstick
- Plasma and urine PK samplings just before second intake of BI 894999 (see 5.4, Flow Chart and Appendix 10.2). No urine PK samplings from protocol version 12.0 onwards

- [redacted])
- Breakfast a half hour before dosing for the food interaction cohort only, for patients who are under fasted conditions on Day 1 of Visit 1 (see Appendix 10.2.2)
- Second oral intake of BI 894999 (maintenance dose in Schedule C)
- Completion of a diary card indicating the intake of BI 894999 with date and hour
- Dispensing of medication bottles for the rest of the cycle if not in the food interaction cohort
- Snack at least 2h post-dose for the food interaction cohort only, for patients who are under fasted conditions on Day 2 of Visit 1 (see Appendix 10.2.2)

Visit 1 on Day 3 for the food interaction cohort only, for both Schedules A and B
- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position before the second study drug intake as specified in the Flow Chart. See also Appendix 10.2.2 for the timing of PK sampling to be performed during PK days (see 5.4 and Flow Chart)
- Plasma PK sampling just before third intake of BI 894999 (see 5.4, Flow Chart and Appendix 10.2)
- Third oral intake of BI 894999
- Completion of a diary card indicating the intake of BI 894999 with date and hour
- Dispensing of medication bottles for the rest of the cycle if in the food interaction cohort

Visit 2 on Day 8 (±1: window only allowed for Schedules A and B) for all Schedules. The tests of this visit can be performed locally by the patient with a phone call visit with the Investigator but all assessments must be performed, after approval of protocol version 12.0, for NC and DLBCL patients in Schedule C.
- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Compliance check for at home BI 894999 intake via medication bottle(s) and diary card completion
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position before the study drug intake
- 12-lead, if possible digitalized triplicate, ECGs taken after at least 5 min rest in supine position. If assessments performed outside the clinical site (after protocol version 12.0 approval), the original tracing of the ECG must be sent to the Investigator who will provide it to the central reading CRO
- Safety laboratory parameters including haematology with differential, biochemistry (with CK and troponin hs) and coagulation parameters
- Plasma PK sample for trough level analysis (before BI 894999 intake for Schedules A and B). Not for NC and DLBCL patients in Schedule C after protocol version 12.0
- Intake of BI 894999 for Schedules A and B only

- Completion of a diary card indicating the intake of BI 894999 with date and hour for Schedules A and B only
- During treatment tumour biopsy for Schedules A and B, between Day 8 and Day 11 (might be moved ahead between Day 3 and Day 8 (see 3.1)), between 4 and 8h post-dose intake of BI 894999 on the day of the biopsy. This biopsy is optional in the escalation phase and in extension of MTD cohort for those patients who consented and mandatory in expansion Phase Ib (for those patients who had a screening tumour biopsy or archived tumour tissue collected) (platelet count and coagulation must be checked prior to each biopsy and must be adequate) (see 3.3.2 and 5.5). The on treatment biopsy may remain optional if no easily accessible lesions are available

Visit 3 on Day 12 (±1) for both Schedules A and B
- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Compliance check for at home BI 894999 intake via medication bottle(s) and diary card completion
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position before the study drug intake
- Plasma PK sample for trough level analysis before BI 894999 intake
- Intake of BI 894999
- Completion of a diary card indicating the intake of BI 894999 with date and hour

Visit 3 on Day 15 for Schedule C
- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position before the study drug intake
- Digitalised, if possible triplicate, 12-lead ECGs taken after at least 5 min rest in supine position before intake of BI 894999
- Intake of BI 894999 loading dose
- Completion of a diary card indicating the intake of BI 894999 with date and hour

Visit 4 on Day 14 for both Schedules A and B
- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Compliance check for at home BI 894999 intake via medication bottle(s) and diary card completion
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position before the study drug intake and then according to the Flow Chart
- Digitalised triplicate 12-lead ECGs taken after at least 5 min rest in supine position before intake of BI 894999 and then at several time points (see 5.3.4 and Flow Chart)
- Safety laboratory parameters including haematology with differential, biochemistry (with CK and troponin hs), and coagulation parameters (including factors II, V, VII and IX in the 20 first patients in Phase Ib), and urinalysis via dipstick

- Whole blood sampling for HEXIM1 (or other genes related to the MOA of BI 894999) gene expression before intake of BI 894999 and then at several time points (see 5.5, Appendix 10.2 and Flow Chart)
- Plasma and urine PK samplings (see 5.4, Flow Chart and Appendix 10.2)
- Intake of BI 894999
- Completion of a diary card indicating the intake of BI 894999 with date and hour.

Visit 4 on Day 15 for Schedule A
- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position 24 h after intake of BI 894999 in Cycle 1, Day 14
- Digitalised triplicate 12-lead ECGs taken after at least 5 min rest in supine position before intake of BI 894999
- Plasma and urine PK samplings (see 5.4, Flow Chart and Appendix 10.2)
- Whole blood sampling for HEXIM1 (or other genes related to the MOA of BI 894999) gene expression at 24h post-dose, just before intake of BI 894999 for that Day (see 5.5, Appendix 10.2 and Flow Chart)
- Intake of BI 894999
- Completion of a diary card indicating the intake of BI 894999 with date and hour

Visit 4 on Day 15 for Schedule B
- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position 24 h after last intake of BI 894999 in Cycle 1, on Day 14
- Digitalised triplicate 12-lead ECGs taken after at least 5 min rest in supine position 24 hours after last BI 894999 intake in Cycle 1, on Day 14
- Plasma and urine PK samplings (see 5.4, Flow Chart and Appendix 10.2)
- Whole blood sampling for HEXIM1 (or other genes related to the MOA of BI 894999) gene expression at 24h, 26h, 28h and 32h post-dose after last BI 894999 intake in Cycle 1, on Day 14 (see 5.5, Appendix 10.2 and Flow Chart)

Visit 4 on Day 18 (±1) for Schedule B
- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position
- Plasma PK sampling for trough level analysis (see 5.4, Flow Chart and Appendix 10.2)
- Whole blood sampling for HEXIM1 (or other genes related to the MOA of BI 894999) gene expression at the time of the visit (see 5.5, Appendix 10.2 and Flow Chart)

Visit 4 on Day 21 for Schedule C
- Changes in concomitant therapy
- Occurrence of AEs since last visit

- Compliance check for at home BI 894999 intake via medication bottle(s) and diary card completion
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position before the study drug intake and then according to the Flow Chart
- Digitalised, if possible triplicate, 12-lead ECGs taken after at least 5 min rest in supine position before intake of BI 894999 and then at several time points (see 5.3.4 and Flow Chart)
- Safety laboratory parameters including haematology with differential, biochemistry (with CK and troponin hs), coagulation parameters and urinalysis via dipstick
- Whole blood sampling for HEXIM1 (or other genes related to the MOA of BI 894999) gene expression before intake of BI 894999 and then at several time points (see 5.5, Appendix 10.2 and Flow Chart)
- Plasma and urine PK samplings (see 5.4, Flow Chart and Appendix 10.2). No urine PK samplings from protocol version 12.0 onwards
- Intake of BI 894999 maintenance dose
- Completion of a diary card indicating the intake of BI 894999 with date and hour.
- Optional during treatment tumour biopsy between Day 18 and Day 21 for those patients who consented, between 4 and 8h post-dose intake of BI 894999 on the day of tumour biopsy (platelet count and coagulation must be checked prior to each biopsy and must be adequate) (see 3.3.2 and 5.5)

Visit 4 on Day 22 for Schedule C

- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position 24 h after last intake of BI 894999 in Cycle 1, on Day 21
- Digitalised, if possible triplicate, 12-lead ECGs taken after at least 5 min rest in supine position 24 hours after last BI 894999 intake in Cycle 1, on Day 21
- Plasma and urine PK samplings (see 5.4, Flow Chart and Appendix 10.2). No urine PK samplings from protocol version 12.0 onwards
- Whole blood sampling for HEXIM1 (or other genes related to the MOA of BI 894999) gene expression at 24h, 26h, 28h and 32h post-dose after last BI 894999 intake in Cycle 1, on Day 21 (see 5.5, Appendix 10.2 and Flow Chart). Only at 24h post-dose for NC and DLBCL patients after protocol version 12.0 approval

Visit 5 on Day 22 for both Schedules A and B, on Day 29 for Schedule C

- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Compliance check for at home BI 894999 intake via medication bottle(s) and diary card completion (done on Day 14 for Schedule B and on Day 21 for Schedule C)
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position
- Digitalised, if possible triplicate, 12-lead ECGs taken after at least 5 min rest in supine position (see 5.3.4 and Flow Chart)
- Safety laboratory parameters including haematology with differential, biochemistry (with CK and troponin hs), and urinalysis by dipstick.

- Plasma PK sample for trough level analysis in Schedule C
- Intake of BI 894999 only for Schedule A if Day 22 is not corresponding to Day 1 of Cycle 2
- Completion of a diary card indicating the intake of BI 894999 with date and hour only for Schedule A if Day 22 is not corresponding to Day 1 of Cycle 2

10.5.2.2 Further Cycles

Visit 1 on Day 1 in all cycles for all Schedules except in Cycle 2 for Schedule B. After approval of protocol version 12.0, for NC and DLBCL patients, starting from Cycle 6, if too difficult for the patient to travel frequently to the clinical site, this visit may happen via a phone call visit between the Investigator and the patient, after all tests are performed locally by the patient and this for all even cycles, if allowed by country regulations and if deemed safe by the Investigator, after discussion with the Sponsor. In this case, medication dispensation may be performed for two cycles at Visit 1 of uneven cycles, starting from Cycle 5 onwards.

- Review of patient's eligibility
- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Physical examination including body weight and ECOG performance score
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position
- 12-lead digitalized, if possible triplicate, ECGs taken after at least 5 min rest in supine position, before intake of BI 894999. If performed locally, the original ECG tracing must be sent to the Investigator who will provide it to the central reading CRO
- Safety laboratory parameters if previous lab older than 48 hours, including haematology with differential, biochemistry (with CK and troponin hs), coagulation parameters, tumour markers if applicable (mandatory PSA for mCRPC patients in Phase Ib), and urinalysis via dipstick
- Pregnancy test for women of childbearing potential
- First oral intake of BI 894999 for the cycle (loading dose in Schedule C)
- Dispensing of medication bottles for the rest of the cycle (see above)

Visit 1 on Day 1 of Cycle 2 for Schedule B

- Review of patient's eligibility
- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Physical examination including body weight and ECOG performance score
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position, before intake of BI 894999
- 12-lead digitalized triplicate ECGs taken after at least 5 min rest in supine position, before intake of BI 894999
- Safety laboratory parameters if previous lab older than 48 hours, including haematology with differential, biochemistry (with CK and troponin hs), coagulation parameters (including factors II, V, VII and IX in the 20 first patients in Phase), tumour markers if applicable (PSA mandatory for mCRPC patients in Phase Ib), and urinalysis via dipstick

- Pregnancy test for women of childbearing potential
- PK blood samplings (see Appendix 10.2 and Flow Chart)
- Whole blood sampling for HEXIM1 (or other genes related to the MOA of BI 894999) gene expression (see Appendix 10.2 and Flow Chart)
- First oral intake of BI 894999 for the cycle

Visit 1 on Day 2 of Cycle 2 for Schedule B
- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position, before intake of BI 894999
- PK blood sampling just before intake of BI 894999 (see Appendix 10.2 and Flow Chart)
- Whole blood sampling for HEXIM1 (or other genes related to the MOA of BI 894999) gene expression just before intake of BI 894999 (see Appendix 10.2 and Flow Chart)
- Second oral intake of BI 894999 for the cycle
- Dispensing of medication bottles for the rest of the cycle

Visit 2 on Day 15 (+2/-4: window allowance only for Schedules A and B): only in Cycles 2, 3 and 4 for both Schedules A and B, for all cycles in Schedule C. All assessments of this visit may be performed locally by the patient with a phone call visit with the Investigator if allowed by local regulations
- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position
- Safety laboratory parameters if previous lab older than 48 hours, including haematology with differential, biochemistry (with CK and troponin hs) and coagulation parameters
- 12-lead, if possible digitalized triplicate, ECGs taken after at least 5 min rest in supine position. If done locally, the original ECG tracing must be sent to the Investigator who will provide it to the central reading CRO
- Intake of BI 894999 second loading dose of the cycle only for Schedule C

Visit 3 on Day 22 in Cycle 2 or Visit 2 on Day 22 in further Cycles for both Schedules A and B, Visit 3 on Day 29 for all cycles in Schedule C
The end of cycle evaluation visit will occur just before to start third cycle. In case the patient does not continue therapy, the results of imaging have to be recorded and the EOT examinations done.
- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Compliance check for at home BI 894999 intake via medication bottle(s)
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position
- 12-lead, if possible digitalized triplicate, ECGs taken after at least 5 min rest in supine position

- Safety laboratory parameters if previous lab older than 48 hours, including haematology with differential, biochemistry (with CK and troponin hs)
- MRI, CT, tumour assessment (by imaging with FDG-PET/CT scan and physical palpation in DLBCL patients): to be performed at the end of every even cycle. For DLBCL patients, the FDG-PET/CT scan is to be performed at the end of Cycle 2, Cycle 4 and every four cycles thereafter.
- Bone scan every four cycles only in mCRPC patients and PSA at the same time-points
- For patients who show an objective response at the imaging evaluation according to RECIST 1.1 for solid tumours (also mCRPC patients with measurable disease according to RECIST 1.1) or according to RECIL 2017 for DLBCL patients or are benefiting from the treatment and who consented for it, fresh tumour biopsy at any time during response (platelet count and coagulation must be checked prior to each biopsy and must be adequate) and/or sending of archival tumour tissue or slides (at least 10 slides)
- Mandatory 2-3 mL EDTA blood DNA sample on the day of tumour biopsy or at any time during response for the patients who undergo a tumour biopsy and/or agree to the sending of archival tumour tissue or slides at objective response or benefit from the treatment
- MUGA scan or echocardiography for LVEF determination only at the end of Cycle 2, always using the same method

10.5.3 End of Treatment (EOT) visit

- Changes in concomitant therapy
- Occurrence of AEs since last visit
- Compliance check if applicable
- Physical examination including body weight and ECOG performance score
- Vital signs including blood pressure, pulse and body temperature, taken after at least 2 min rest in supine position
- 12-lead, if possible digitalized triplicate, ECGs taken after at least 5 min rest in supine position if previous one older than 48 hours
- MUGA scan or echocardiography for LVEF determination (always using the same method), if not performed in the last 6 weeks and the patient's health status allows to do so
- Safety laboratory parameters if previous lab older than 48 hours, including haematology with differential, biochemistry (with CK and troponin hs), coagulation parameters, and urinalysis via dipstick
- β-HCG pregnancy test for women of childbearing potential
- MRI, CT, tumour assessment (by imaging and physical palpation in DLBCL patients): to be performed if not done within the past 6 weeks
- Overall clinical benefit assessment by the Investigator for NC patients only
- Registration of termination date for study medication

10.5.4 Follow-up (FU) visit

The first FU visit (EOR) must occur 30 days (+7 days) after the last intake of BI 894999. A repeated FU must take place at least every 12 weeks for any necessary follow-up of an AE or until disease progression, lost to follow-up, treatment with another anti-cancer therapy or end

of the whole trial as specified in Section 8.6. If the patient is unable to attend a site visit, at least information on AEs and patient's status must be obtained by a phone contact.

- Changes in concomitant therapy for all changes until 30 days after last BI 894999 intake, thereafter, only if taken to treat a study-treatment emergent AE
- Occurrence of all AEs since last visit until 30 days after the last BI 894999 intake, thereafter, only AEs which are considered study drug related.
- Physical examination including ECOG performance score
- 12-lead digitalized triplicate ECGs taken after at least 5 min rest in supine position (optional)
- Safety laboratory parameters if previous lab older than 48 hours, including haematology with differential, biochemistry (optional) and coagulation parameters (if abnormal at EOT)
- MRI, CT, tumour assessment (by imaging and physical palpation in DLBCL patients): to be performed if not done within the past 6 weeks
- MUGA scan or echocardiography for LVEF determination (optional) (always using the same method)
- Patient's status. For NC patients who consented to do so, overall survival status will continue to be collected until death, withdrawal of consent to further collect the information, lost to follow-up or until 12 months after the end of the trial, whichever comes first.

10.6 CLINICALLY RELEVANT CYP1A2, CYP2C8, CYP3A4 SUBSTRATES:

Table 10.6: 1: list of medications considered clinically relevant substrates of CYP 1A2, CYP 2C8 and CYP3A4

CYP1A2	rosiglitazone	dasatinib	midostaurin
alosetron	torsemide	dexamethasone	naloxegol
amitriptyline	**CYP3A4**	diazepam	nateglinide
caffeine	alfentanyl	diltiazem	nelfinavir
clomipramine	alisporivir	docetaxel	neratinib
clozapine	almorexant	domperidone	nifedipine
duloxetine	alpha-dihydroergocryptine	dronaderone	nisoldipine
estradiol	alprazolam	ebastine	ondansetron
fluvoxamine	aplaviroc	eletriptan	paritaprevir
haloperidol	aprepitant	eliglustat	perospirone
imipramine N-DeMe	aripripazole	elvitegravir	pimozide
melatonin	atazanavir	eplerenone	quetiapine
olanzapine	atorvastatin	estradiol	quinidine 3OH
ondansetron	avanafil	everolimus	ridaforolimus
pirfenidone	blonanserin	felodipine	rilpivirine
ramelteon	bosutinub	fentanyl	risperidone
ramosetron	brecanavir	finasteride	ritonavir
riluzole	brotizolam	gleevec	rivaroxaban
selegiline	budesonide	grazoprevir	salmeterol
tacrine	buspirone	haloperidol	saquinavir
tasimelteon	cafergot	ibrutinib	sildenafil
theophylline	caffeine	indinavir	simeprevir
tizanidine	capravirine	irinotecan	simvastatin
verapamil	casopitant	isavuconazole	sirolimus
(R)warfarin	cerivastatin	ivabradine	tacrolimus
zileuton	cilostazol	ivacaftor	tadalafil
zolmitriptan	clarithromycin	levomethadyl	tamoxifen
CYP2C8	cobimetinib	lomitapide	telithromycin
amodiaquine	cocaine	lopinavir	terfenadine
cerivastatin	codeine-Ndemethylation	lovastatin	ticagrelor
dasabuvir	conivaptan	lumefantrine	tilidine
montelukast	cyclosporine	lurasidone	tipranavir
paclitaxel	danoprevir	maraviroc	tolvaptan
pioglitazone	darifenacin	methadone	trazodone
repaglinide	darunavir	midazolam	triazolam

Table 10.6: 1: list of medications considered clinically relevant substrates of CYP 1A2, CYP 2C8 and CYP3A4 (continued)

CYP 3C4 (continued)	venetoclax	vincristine	ziprasidone
ulipristal	verapamil	voclosporin	zolpidem
vardenafil	vicriviroc	zaleplon	

10.7 RECIL 2017 RESPONSE CRITERIA AND DEAUVILLE SCORE

Table 10.7: 1 RECIL 2017: response categories

(R17-3378)

Table 1. RECIL 2017: Response categories based on assessment of target lesions

	% Change in sum of diameters of target lesions from nadir				
	CR	**PR**	**MR[a]**	**SD**	**PD**
% change from baseline	• Complete disappearance of all target lesions and all nodes with long axis <10mm. • ≥30% decrease in the sum of longest diameters of target lesions (PR) with normalization of FDG-PET	≥30% decrease in the sum of longest diameters of target lesions but not a CR	≥10% decrease in the sum of longest diameters of target lesions but not a PR (<30%)	<10% decrease or ≤ 20% increase in the sum of longest diameters of target lesions	• >20% increase in the sum of longest diameters of target lesions • For small lymph nodes measuring <15 mm post therapy, a minimum absolute increase of 5 mm and the long diameter should exceed 15 mm • Appearance of a new lesion
FDG-PET	Normalization of FDG-PET (Deauvile score 1-3)	Positive (Deauville score 4-5)	Any	Any	Any
Bone marrow involvement	Not involved	Any	Any	Any	Any
New lesions	No	No	No	No	Yes or No

CR, complete response; CT, computerized tomography; FDG-PET, [^{18}F]2-fluoro-2-deoxy-D-glucose; MR, minor response; PD, progression of disease; PR, partial response; SD, stable disease.
[a]A provisional category.

Table 10.7: 2 Deauville scoring system for FDG/PET scan evaluation according to RECIL 2017

(R17-3376)

Table 1 Five-point scoring system developed for the RATHL trial

Note: If mediastinal blood pool activity is equal to or greater than activity in the liver, then the uptake within the lesion should be compared with that in the liver (uptake lesion < liver *score 2*; lesion = liver *score 3*)

Score	PET/CT scan result
1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately increased compared to the liver at any site
5	Uptake markedly increased compared to the liver at any site
X	New areas of uptake unlikely to be related to lymphoma

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Number of global amendment		1
Date of CTP revision		02 Sep 2015
EudraCT number		2015-001111-12
BI Trial number		1367.1
BI Investigational Product(s)		BI 894999
Title of protocol		An open label, Phase Ia/Ib dose finding study with BI 894999 orally administered once a day in patients with advanced solid tumours, with repeated administration in patients with clinical benefit
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		X – notification was made on the 27th of Jul 2015 to the Competent Authorities and Ethics Committees about the precautionary measure taken due to potential CYP inducing effect (3A4, 2C8 and 1A2) of BI 894999 further to a non-clinical finding.
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		1.2.2, 3.3.2 point 6, 4.2.2, addition of Appendix 10.6 Further to additional pre-clinical results, Flow Charts, 3.1.1, 5.5, 7.3.6, 10.2, 10.5 This protocol revision is also the opportunity to add clarification to some other sections: - 3.1 - 3.1.1 - 4.3 - 5.3.6.1 - [redacted] - 5.5 - 6.2.1 - 8.4.1

Description of change		-1.2.2: Addition of the pre-clinical findings of potential drug inducing effect of BI 894999 on CYP3A4, 1A2 and 2C8 - 3.3.2: precision in inclusion criterion 6 that women of childbearing potential using a contraceptive pill as a method of birth control need to add a barrier method - 4.2.2: potential drug inducing effect of BI 894999 on CYP3A4, 1A2 and 2C8 with possible result of reduction of plasma concentrations of concurrent medications which are substrates of these CYP enzymes, including contraceptive pills and the potential resulting decrease of their effectiveness: caution added in 4.2.2.1 about the use of concomitant medication which are substrates, request for women of childbearing potential using a contraceptive pill to add a barrier method in section 4.2.2.3 - Appendix 10.6: Addition of non-exhaustive list of CYP 3A4, 2C8 and 1A2 substrates Further to additional pre-clinical findings: Addition of whole blood samples for HEXIM1 gene expression analyses at 24h post-dose of BI 894999 intake on Days 1 and 14 of Cycle 1 and deletion of all peripheral blood mononuclear cells (PBMC) samples for HEXIM1 protein expression in Flow Charts, Sections 3.1.1, 4.1.4.1, 5.5, 6.2, 7.3.6, 10.2, 10.5 Additional changes: - Section 3.1: - If no patient from first cohort experiences a drug-related CTCAE grade ≥2, the dose may be increased from 0.2 mg to 1 mg in second cohort and if no patient from second cohort experiences a drug-related CTCAE grade ≥2, the dose may be increased from 1 mg to 5 mg in third cohort - Extension to more patients in a cohort due to a drug-related CTCAE grade ≥2 will only apply if the AE happens in a single patient cohort - Section 3.1.1 DMC membership is given *in extenso* in the DMC charter, apart from the protocol - Section 4.3:

		The compliance calculation will be done by counting the number of tablets from each strength actually taken x100 divided by the number of tablets from each strength which should have been taken - Section 5.3.6.1: DLT definitions: last bullet: any drug-related adverse event preventing from taking his treatment according to the given schedule (more than 2 consecutive doses missed): this concerns the AEs except those described in the 4 previous bullets of DLTs definitions. "Protocol-specified significant events": this term is replaced by "AESIs" Intensity of Adverse Events: "intensity" is replaced by "severity" - [redacted] - Section 6.2.1: For the medical history, the number of metastatic sites will not be requested anymore - Section 8.4.1: the term "side effect" is replaced by "adverse reaction"
Rationale for change		New pre-clinical findings need to be provided to the investigators and patients to make them aware of potential drug-drug interactions, specifically in relation to the contraceptive pill if this is being taken by women of child-bearing potential. This amendment includes additional safety measures in women of childbearing potential to not only rely on contraceptive pills for contraception, but they have to also use a barrier method of contraception as well. Further additional preclinical PK/Pharmacodynamics modelling work showed the dynamics of HEXIM 1 (as a pharmacodynamics marker) over a 24 hour period post-dosing. Given this new data, adding an extra sampling time point at 24h post-dose (on Day 1 and Day 14) would help understand the dynamics of HEXIM 1 in patients. Since the PBMC sampling (for analysis of HEXIM 1 protein) is only performed at 24h post-dose, this does not provide

		information about the dynamics of HEXIM 1 induction over the 24h period post-dose, the PBMC collection is therefore not considered to be of additional value to the biomarkers analysis and is removed from the protocol.
		
		Additional changes:
		- Section 3.1:
		  - Clarification for the escalation rules used from first to second cohort and from second to third cohort
		  - Clarification on which cohorts are concerned by addition of patients in case of drug-related CTCAE grade ≥ 2 and how many patients needed under BLRM, once a drug-related CTCAE grade ≥ 2 occurred in Cycle 1
		- Section 3.1.1:clarification where to find *in-extenso* DMC membership
		- Section 4.3: clarification on the way to calculate the compliance due to the different possible tablet strengths
		- Section 5.3.6.1:
		  Clarification on DLT definitions to make sure there is common and same understanding for everyone
		  "Protocol-specified significant events" is a term that is not used anymore in the protocol and corresponds to the term "AESIs" used for this protocol.
		  Intensity of AE: as the CTCAE grading is a severity scale, the term "severity" is more appropriate.
		- [redacted]
		- Section 6.2.1: as the metastatic sites are described, there is no need to have the number in addition for the study interpretation of results
		- Section 8.4.1: as the drug is not yet marketed, there are not yet known side effects and the term "adverse reaction" is the appropriate term

11.2 GLOBAL AMENDMENT 2

Number of global amendment		2
Date of CTP revision		08 Apr 2016

EudraCT number		2015-001111-12
BI Trial number		1367.1
BI Investigational Product(s)		BI 894999
Title of protocol		An open label, Phase Ia/Ib dose finding study with BI 894999 orally administered once a day in patients with advanced malignancies, with repeated administration in patients with clinical benefit
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Title, synopsis, Flow Charts, 1.2.1, 2.1, 2.2, 2.3, 3.1, 3.1.1, 3.2, 3.3.1, 3.3.2, 3.3.3, 3.3.4, 4.1.1, 4.1.2, 4.1.3, 4.1.4, 4.2.1, 4.2.2, 5.1.1, 5.1.2, 5.3.6, 5.4.5, 5.5.1, 6.1, 6.2, 7.1, .1, 7.3.27.3.6, 7.4, 7.7, 9, 10.2, 10.3, 10.4, 10.5
Description of change		Changes across all these sections concern: - The addition of a second Schedule, Schedule B, of intermittent administration of trial medication (two weeks on, one week off in 3-week cycles) in solid tumours in order to also determine the MTD with this Schedule. The Schedule B dose finding will run in parallel to Schedule A in patients with solid tumours, starting from the highest dose tested in Schedule A in patients with solid tumours and considered safe to start with by the DMC - The Schedule A of continuous dosing of trial medication (in 3-week cycles) will be administered in patients with solid tumours in order to determine the MTD with this Schedule and, starting from this MTD minus one dose level, an additional cohort of NHL patients will be included with

		Schedule A in order to determine the MTD in patients with NHL. Once the MTD is determined in this NHL cohort, the cohort will be further extended at MTD until a total of 15 up to 27 patients are included in the NHL cohort. The addition of the NHL cohort also leads to the change from "advanced solid tumours" to a more global designation of "advanced malignancies" in the title of the study to include both solid tumours and hematologic malignancies of the NHL type. - Once the MTD is determined for both Schedules A and B in patients with solid tumours, the DMC will determine the best Schedule and the MTD cohort of the chosen Schedule will be further extended up to 12 patients These changes imply - the introduction of specific Flow Charts for Schedule B with additional days of visits and additional PK and pharmacodynamics tests to be performed in Cycles 1 and 2 - the addition of pre-clinical information on tests performed in lymphoma and the rationale to test this BET inhibitor in patients with Non-Hodgkin lymphoma as well - the addition of MTD determination for Schedule B and for the NHL cohort in the objectives and in the endpoints - the addition of specific inclusion and exclusion criteria for the NHL cohort - the specification on how to capture oncological history for NHL patients - the addition of physical tumour evaluation of NHL patients - the introduction of the notion of Tumour Lysis Syndrome (TLS) prevention left to investigator's judgement, in NHL patients - the addition of specific DLT definitions for NHL patients - the change in sample size Additional changes: - Synopsis, Section 5.12, Section 5.1.3: to decrease

		the number of secondary PK endpoints, some of the PK endpoints are now considered as further endpoints - Section 3.3.3.1, point 13: the steroids are allowed for palliative intent at study entry provided they are given at a stable dose for the four weeks before study screening - Section 4.1.4.1: - During the first cycle, a drug-free interval (not including the one week schedule treatment break in Schedule B) may only occur in case of a DLT or at the end of the evaluation period of 21 days, for recovery of another drug-related AE of CTCAE grade 3 or 4 - Section 4.1.4.2: Treatment with the trial drug has also to be discontinued temporarily in case of another drug-related AE of CTCAE grade 3 or 4 than a DLT to allow recovery to at least CTCAE grade 1 or baseline level (except CTCAE grade 2 peripheral sensory neuropathy as well as CTCAE grade 2 anaemia or lymphopenia) They may then re-start at the same dose. - Section 4.2.1: steroids are allowed for treatment of adverse reactions or tumour-associated symptoms but should be kept at the lowest possible dose for the shortest possible duration if introduced during study treatment period - Section 5.3.4 - correction of Bazett's and Fridericia's formulas - Section 5.3.6.1: - DLT definitions: last bullet for solid tumours: a drug-related grade 2 oral mucositis/stomatitis preventing from taking his treatment according to the given schedule (more than 2 consecutive doses missed) - Instructions for reporting of new cancers of new histology - Sections 5.3.7 and 8.4.2: Additional information on Investigator's and BI obligations for SAE and/or AESI reporting - Sections 5.4.5, 5.5.1.2, 5.5.1.2.2, 7.3.6, 7.4, 10.5: when the pharmacodynamics exploration speaks about modulation of HEXIM1 gene expression, it will also include additional other genes related to the MOA of BI 894999 - Flow Charts for both Schedules and Sections 3.1,

		3.3.1, 5.5.1.1.1, 5.5.1.2: for patients who are responding to the treatment (objective response according to RECIST 1.1) or have a clinical benefit and if they have given consent for it, optional collection of archival tumour tissue and/or fresh tumour biopsy at the time of response or benefit for additional analyses centred around but not limited to the MOA of BI 894999 and the molecular nature of the disease. Analyses will include both RNA and DNA analysis in an attempt to identify biomarkers of efficacy. In case tumour tissue is given, a mandatory 2-3 mL EDTA blood DNA sample will be obtained from those patients - Flow Charts for both Schedules and Sections 3.1, 3.3.1, 5.5.1.1.1, 5.5.1.2: fresh tumour biopsies at screening and at steady state in Cycle 1 are now optional for the whole Phase Ia, including the extension cohort at MTD and remain mandatory for the phase Ib patients
Rationale for change		- Addition of a second Schedule with intermittent dosing: this was already foreseen as a possibility in the first version of the protocol in case of intolerability of the continuous dosing schedule. As 2 DLTs occurred in 2 patients treated at a dose of 5 mg which is lower than expected from pre-clinical models, the DMC decided to also test in parallel an intermittent dosing schedule in an attempt to improve tolerability of BI 894999. - Addition of a NHL cohort: additional pre-clinical investigations both *in vitro* and *in vivo* have shown activity in lymphoma, particularly NHL. Recent preliminary data of Phase I trials with other BET inhibitors have also reported promising results in patients with NHL. Both pre-clinical data with BI 894999 and clinical results from other BET inhibitors warrant further investigation with BI 894999 in patients with NHL. Additional changes - Synopsis and sections 5.1.2 and 5.1.3: according to BI standards, there should not be more than 10 secondary endpoints and each PK endpoint is considered separately. For this reason, the secondary PK endpoints were limited with some PK parameters becoming further endpoints.

		- Sections 3.3.3.1, point 13 and 4.2.1: the steroids must be given at a stable dose for the four weeks before study screening and kept at the minimum if introduced during study treatment period to avoid as much as possible interference with the RECIST evaluation - Section 4.1.4.1: - During the first cycle, a drug-free interval (not including the one week schedule treatment break in Schedule B) may only occur in case of a DLT or drug-related CTCAE grade 3 or 4 at the end of the evaluation period of 21 days: clarification that a drug free interval in the first cycle (other than the normal scheduled one in Schedule B) is not allowed except when the patient experiences a DLT or a drug-related CTCAE grade 3 or 4 at the end of the 21 days period of the first cycle - Section 4.1.4.2: clarification of treatment break at the end of a cycle for drug-related AE of CTCAE grade 3 or 4 to be consistent with instructions given in Section 3.1. - Section 5.3.4 - correction of an error in Bazett's and Fridericia's formulas - Section 5.3.6.1: - DLT definitions: last bullet for solid tumours: a drug-related grade 2 oral mucositis/stomatitis preventing the patient from taking his treatment according to the given schedule (more than 2 consecutive doses missed): clarification of this DLT definition to avoid misinterpretation with a too broad definition which would make any drug-related AE a possible DLT - Instructions for reporting of new cancers of new histology: according to BI new protocol template - Sections 5.3.7 and 8.4.2: changes to conform with new BI protocol template regarding SAEs/AESI reporting obligations - Sections 5.4.5, 5.5.1.2, 5.5.1.2.2, 7.3.6, 7.4, 10.5: when the pharmacodynamics exploration speaks about modulation of HEXIM1 gene expression, it will also include additional other genes related to the MOA of BI 894999: clarification that the gene expression analysis will not be limited to only HEXIM1 gene expression but also to other genes

		related to the MOA of BI 894999, according to actual scientific knowledge - Flow Charts for both Schedules and Sections 3.1, 3.3.1, 5.5.1.1.1, 5.5.1.2: for patients who are responding to the treatment (objective response according to RECIST 1.1) or have a clinical benefit and if they have given consent for it, optional collection of archival tumour tissue and/or fresh tumour biopsy at the time of response or benefit: this will allow further understanding of the mechanism of action of the BET inhibitor and its interaction with certain tumour types - Flow Charts for both Schedules and Sections 3.1, 3.3.1, 5.5.1.1.1, 5.5.1.2: fresh tumour biopsies at screening and at steady state in Cycle 1 are now optional for the whole Phase Ia, including the extension cohort at MTD and remain mandatory for the phase Ib patients: the pharmacodynamics information that would be gained from all comers tumours in the phase Ia part would be limited and would not compensate for the burden to the patients

11.3 GLOBAL AMENDMENT 3

Number of global amendment		3
Date of CTP revision		23 Nov 2016
EudraCT number		2015-001111-12
BI Trial number		1367.1
BI Investigational Product(s)		BI 894999
Title of protocol		An open label, Phase Ia/Ib dose finding study with BI 894999 orally administered once a day in patients with advanced malignancies, with repeated administration in patients with clinical benefit
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		– Notification was made on the 7th of Oct 2016 to the Competent Authorities and Ethics Committees about the precautionary measures taken due to cardiac findings in patients already participating in the trial.
Can be implemented without IRB / IEC / Competent		

Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Flow Charts, 1.2.3, 2.3, 5.3.3, 5.3.4, 5.3.5, 6.2, 6.1, 10.4, 10.5

Description of change		In sections: Flow Charts, 1.2.3, 2.3, 5.3.3, 5.3.4, 5.3.5, 6.2, 6.1, 10.4, 10.5
		- Each time a safety laboratory sampling is performed, addition of CK-MB and mandatory troponin T hs level determination even if normal CK results
		- Each time an ECG is performed, it has to be acquired as triplicate digitalized 12-lead ECG with the CRO device and sent to CRO for central reading
		- Addition of a visit every week, starting from Cycle 2 onwards with the following examinations to be performed at these visits:
		  - Occurrence of AEs since last visit
		  - Changes in concomitant medications since last visit
		  - Digitalized triplicate ECGs to be sent to central reading CRO for review by cardiologist and interval measurements
		  - Safety laboratory blood sampling for determination of at least CK, CK-MB and troponin T hs levels and any other additional parameter judged to be controlled by the investigator

Rationale for change		These measures were taken as urgent safety measures at the time when some cardiac findings were observed in some patients included in the trial and before the cardiologic findings were evaluated by an external expert cardiologist to try to understand their clinical significance. This is applicable to the ongoing patients who are shown to benefit from the treatment in order to allow them to continue the treatment under close cardiac safety monitoring. Any further recruitment is stopped in the trial.

11.4 GLOBAL AMENDMENT 4

Number of global amendment		4
Date of CTP revision		12 May 2017
EudraCT number		2015-001111-12
BI Trial number		1367.1
BI Investigational Product(s)		BI 894999
Title of protocol		An open label, Phase Ia/Ib dose finding study with BI 894999 orally administered once a day in patients with advanced malignancies, with repeated administration in patients with clinical benefit
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Synopsis, Flow Charts, 2.2, 2.3, 3.1, 3.2, 3.3.3.2, 4.1.1, 4.1.2, 4.1.4, 4.1.6, 5.1.1.1, 5.1.2, 5.3.3, 5.3.5.1, 5.3.6.1, 6.1, 7.1, 7.3.1, 7.3.2, 8.6, 10.5
Description of change		Section 2.3: - Results of the external cardiology review showed that a small increase in serum troponin, temporally related to drug administration was observed in some patients. There was no observed clinically relevant QT prolongation, no suggestion of any rate change, conduction abnormality or evidence of drug-induced ischaemia. - Thrombocytopenia is considered an expected AE associated with BI 894999. Synopsis, Flow Charts for both Schedules, Sections 2.3, 5.3.3, 5.3.5, 6.2, 10.4, 10.5: - - Triplicate digitalized ECGs will happen once a week during Cycle 1 (addition of

		this examination at Day 8 visit) - In Cycle 2, as well as in Cycles 3 and 4, in addition to the first visit of the Cycle, one intermediate visit is foreseen at Day 15 (window of -4 or +2 days) where collection of digitalized triplicate ECGs and measures of CK and troponin T hs will happen. CK-MB is no more systematically requested together with CK measures. From Cycle 5 onwards, the intermediate visit of Day 5 becomes optional - The LVEF evaluation will be performed at screening for all new patients in the trial and will serve as baseline. An evaluation during treatment will then be performed at the end of Cycle 2 and if compatible with the patient's health status, also at the EOT. Synopsis, Sections 2.2, 3.1, 3.2, 4.1.2, 4.1.4, 5.1.1, 5.1.2, 6.1, 7.1, 7.3.1, 7.3.2, 10.3: - Patients in the NHL cohort will be treated with the Schedule selected by the DMC once MTD has been determined for both Schedules A and B in patients with solid tumours. Additional changes in this revised version of the protocol: - Section 3.3.3.2: exclusion criterion 12 in NHL patients includes no myocardial infarction within 6 months prior to study entry - Sections 4.1.1and 4.1.6: availability of 2 mg tablets - Section 5.3.6.1, definition of DLTs: precision that the possible treatment break of 14 days in Schedule A or 21 days in Schedule B at the end of a Cycle does not count in the period of more than 2 consecutive doses missed for DLT definition
Rationale for change		Section 2.3: Assessment by external cardiologists concluded that the cause of this troponin elevation is unclear. Due to the low magnitude of elevations and the

		lack of associated cardiac findings in these patients, the cardiac findings do not preclude further clinical development. Patients may continue on treatment with appropriate monitoring Synopsis, Flow Charts for both Schedules, Sections 2.3, 5.3.3, 5.3.5, 6.2, 10.4, 10.5: Cardiac monitoring was adapted to balance the need to continue close cardiac monitoring and the burden for the patients benefiting from prolonged treatment to have to come too frequently to the clinic. Synopsis, Sections 2.2, 3.1, 3.2, 4.1.2, 4.1.4, 5.1.1, 5.1.2, 6.1, 7.1, 7.3.1, 7.3.2, 10.3: Since this study will serve for a go/no go decision in further development of BI 894999 in NHL patients, it is important that the patients in the NHL cohort in this study are treated with the Schedule selected by the DMC in order to determine the recommended phase II dose in this patient population in case of further development in this indication. Other changes were incorporated to clarify or adapt the protocol, - such as the exclusion criterion of recent myocardial infarction in NHL patients to reflect the same exclusion criterion than for patients with solid tumours - the availability of 2 mg tablets as confirmed with an amendment to the IMPD, already submitted - or the clarification of which period is considered for DLT in case more than two doses are missed.

11.5 GLOBAL AMENDMENT 5

Number of global amendment		5
Date of CTP revision		18 Oct 2017
EudraCT number		2015-001111-12
BI Trial number		1367.1
BI Investigational Product(s)		BI 894999
Title of protocol		An open label, Phase Ia/Ib dose finding study with BI 894999 orally administered once a day in patients with advanced malignancies, with repeated

		administration in patients with clinical benefit
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Synopsis, Flow Charts, 1.1, 1.2.1, 2.1, 2.2, 2.3, 3.1, 3.1.1, 3.2, 3.3.1, 3.3.2.1, 3.3.2.2, 3.3.3.1, 3.3.1.2, 4.1.2, 4.2.1, 4.2.2.1, 4.3, 5.1, 5.2.1, 5.3.1.1, 5.3.3, 5.3.6.1, 5.5, 5.7, 6.1, 6.2, 7.1, 7.3.1, 7.3.2, 7.3.3.2, 7.3.6, 7.4, 7.7, 8.6, 9., 10.3, 10.5, 10.7

Description of change		- In Synopsis, Flow Charts, 2.2, 2.3, 3.1, 3.1.1, 3.2, 3.3.1, 3.3.2.2, 3.3.3.2, 4.1.2, 4.2.1, 4.2.2.1, 5.1, 5.2.1, 5.3.1.1, 5.3.6.1, 5.7, 6.1, 6.2, 6.2.1, 7.1, 7.3.1, 7.3.2, 7.7, 9., 10.3, 10.5, 10.7:
		  - The NHL cohort will be restricted to DLBCL patients. The tumour assessment in this patient population will be based on RECIL 2017 criteria with FDG-PET/CT scans
		  - Previous treatment with a BET inhibitor is added as an exclusion criterion
		  - The medical history will include specificities for DLBCL
		  - Statistical analysis gives precisions when MTD is considered reached in the DLBCL indication
		  - The interim analysis for LSLV primary endpoint will be based only on patients with solid tumours in Phase Ia and not including the DLBCL cohort
		  - Appendix 10.7 describes the response criteria according to RECIL 2017 in DLBCL patients
		- In Synopsis, Flow Charts, 1.1, 1.2.1, 3.1, 3.1.1, 3.2, 3.3.1, 3.3.2.1, 3.3.3.1, 4.1.2, 4.2.1, 5.1.2,

		5.1.3, 5.2.1, 5.5.1, 5.7, 6.1, 6.2, 7.1, 7.3.2, 7.3.3.2, 7.4, 7.7, 9, 10.5: - Specification of the four tumour types selected for the Phase Ib: SCLC, mCRPC, CRC and NC - Explanation on the way to perform tumour assessments in mCRPC patients when patients have non-evaluable disease according to RECIST 1.1, with the addition of bone scans and PSA measures for tumour assessment according to PCWG3 - Description of additional pre-clinical work performed on these indications - Sample size description for each of the four cohorts in Phase Ib - Addition of specific selection criteria: biopsies not mandatory for mCRPC patients who only have bone metastases and for NC patients, specific inclusion criteria for mCRPC patients, extension of exclusion criteria to patients with previous BET inhibitor treatment, allowance of concomitant LHRH antagonists - Addition of specific endpoints for mCRPC patients, based on PSA and radiological PFS and explanation on tumour assessment for this patient population - Description of the 2-stage Bayesian Hierarchical Model (BHM) approach that will be used for the Phase Ib with a futility analysis after 9 patients in each cohort. - Addition of further efficacy analyses in the mCRPC patients cohort based on PSA values - Added reference on PCWG3 - In Flow Charts, 2.3, 5.3.3, 10.5: - Coagulation parameters measured more frequently with addition of measures on first visit of each new cycle and at EOT - Synopsis: the analysis of the primary endpoint of Phase Ib will happen when the last ongoing patient will have reached the 4 cycles of treatment or stopped trial treatment and underwent EOR visit. The report will then be updated when the end of trial is reached. - In 4.3: the compliance limits are now set

		between 80 and 100% - In 5.3.6.1, DLT definition both for solid tumours and DLBCL patients was clarified for electrolytes abnormalities to specify that a control must be performed at 72h for precision of duration of the grade 3. - In 5.5.1.2: specification of the type of tumour biopsies requested (fresh or from archival tissue) and for which patients as well as the method of preparation (FFPE instead of fresh frozen) and the type of analytical determinations on the tumour samples
Rationale for change		Restriction of the NHL to a DLBCL cohort will allow analyses of results in a more homogeneous patient population. RECIL 2017 was set up for lymphoma evaluation. It will be more specific than RECIST 1.1 for evaluation in DLBCL although easier to use than Cheson criteria. The choice of the four types of solid tumours to test in Phase Ib is based on additional pre-clinical work. Almost half of the mCRPC patients will only present with bone metastases, hence necessitating specific tumour assessments based on bone scans and PSA evaluation when RECIST 1.1 would not be useable because of absence of target lesions to follow-up. The increase frequency of monitoring for coagulation parameters is based on observation of factor VII decrease with another BET inhibitor as this might be a class effect. The analysis of the primary endpoint in Phase Ib will happen without waiting for last patient last visit to allow earlier decisions on further development based on these results. The use of 2-stage BHM approach with futility analysis after 9 patients in each patient cohort of Phase Ib will allow closing a cohort earlier if no efficacy signals are seen and avoid unnecessary exposure of additional patients of the same patient population.

		The upper compliance limit is now set at 100% because the patient must be reminded as soon as he/she would take more than requested per protocol. The delay for controlling electrolytes abnormalities will avoid having to consider grade 3 drug related abnormalities as DLTs because no control was performed at 72 h to determine the duration of the grade 3. Additional biomarkers' testing has shown that FFPE biopsies are suitable for analyses, which is an easier handling of samples for shipments. Biomarkers analyses will follow the evolution of knowledge on BET inhibition mechanism of action.

11.6 GLOBAL AMENDMENT 6

Number of global amendment		6
Date of CTP revision		25 Jun 2018
EudraCT number		2015-001111-12
BI Trial number		1367.1
BI Investigational Product(s)		BI 894999
Title of protocol		An open label, Phase Ia/Ib dose finding study with BI 894999 orally administered once a day in patients with advanced malignancies, with repeated administration in patients with clinical benefit
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Flow Charts Schedule B, 2.3, 3.1, 3.3.1, 3.3.2.1, 3.3.3.1, 4.1.4.1, 4.1.4.3, 4.2.1, 5.3.3, 5.3.6.1, 5.5.1.2, 7.3.6, 9, 10.5.1, 10.5.2

Description of change		Safety lab parameters in Flow Charts Schedule B and Sections 2.3, 3.1, 4.2.1, 5.3.3, 10.5.2.1, 10.5.2.2: - Addition of measurement of coagulation parameters: aPTT, PT in seconds and INR on C1D8, day of tumour biopsy in C1 if different day than C1D8, on C1D14 and on Day 15 in C2, C3 and C4 - glucose measurements must happen in fasting condition after an overnight fast - Addition of evaluation of coagulation factors II, V, VII and IX on C1D1 pre-dose, on C1D14 and on C2V1D1 in 20 patients. - In case of thrombocytopenia of CTCAE grade 4, mandatory prophylactic platelet transfusion when platelet count below 20 000/mm^3 Tumour biopsy: Flow Charts in Schedule B, 2.3, 3.1, 3.3.1, 4.1.4.1, 5.5.1.2, 7.3.6 - Change of tumour biopsy in C1 under treatment with BI 894999 from between Day 11 and Day 14 to between Day 8 and Day 11. Further change to between Day 3 and Day 8 of C1 in case the tumour biopsy cannot happen in 5 of the 20 first patients because of abnormal coagulation and/or a platelet count below 50 000/mm^3 on the day of tumour biopsy when performed between D8 and D11. - Need for coagulation parameters (aPTT, PT in sec and INR) to be within normal ranges on the day of biopsy for biopsy to be performed and no request for biopsies in patients with therapeutic level of INR due to treatment with vitamin K antagonist or a novel oral anticoagulant - Clarification that tumour biopsy must happen between 4h and 8h after drug intake - Clarification that tumour biopsy should be taken from same lesion at baseline and under treatment in C1 whenever possible and when applicable Sections 4.1.4.3 and 3.3.3 - Clarification on when to interrupt BI 894999 and when to reduce the dose

		Clarification in handling of a drug-related CTCAE grade 3 troponin increase is seen: interruption of study medication and additional cardiac testing to rule out a new emerging cardiotoxicity. If ruled out, the treatment may be resumed at a reduced dose (DLT rule). Intensified cardiac monitoring will be performed in these cases by evaluation of LVEF before the re-start of treatment and every 2 cycles thereafter to detect any new impaired wall motility or an indisputable drop of LVEF (percentage points reduction of ≥10 from baseline value or drop of LVEF below 50%, corresponding to a CTCAE grade 2) which would lead to drug discontinuation. - Addition of exclusion criterion of LVEF lower than 50% Other changes: - Section 3.3.3.1: NC patients may have a performance status of 2 for inclusion and may have already been treated with another BET inhibitor prior to study entry. - Flow Charts in Schedule B, 10.5.1, 10.5.2.2: suppression of mandatory bone aspirate and biopsy in DLBCL patients in screening in case of negative FDG-PET uptake in bone marrow and during treatment, if a CR is seen.
Rationale for change		Safety lab parameters: - Additional coagulation measures and evaluation of coagulation factors II, V, VII and IX: decrease of coagulation factor VII has been described with other BET inhibitors. Monitoring of coagulation parameters in the 1367.1 study revealed that some patients present with mild prolongation of prothrombin time (PT) and increase in international normalized ratio (INR) on Day 14 of Cycle 1. The additional measures are taken to better characterize the possible influence of BI 894999 on coagulation - Hyperglycaemia has been described with other BET inhibitors. The fact to mandate fasting glucose measures after an overnight fast will allow to characterize a possible

		influence of BI 894999 on the glycaemia - To prevent the risk of bleeding related to BI 894999 induced thrombocytopenia, the protocol recommends a platelet transfusion for any platelet count below 20 000/mm^3 Tumour biopsy: Since the monitoring of coagulation parameters in the 1367.1 study revealed that some patients present with mild prolongation of prothrombin time (PT) and increase in international normalized ratio (INR) on Day 14 of Cycle 1 which is the time at which biopsy under treatment was foreseen, tumour biopsies will only be performed if the platelet count is above 50 000/mm^3 without the support of a transfusion and coagulation parameters (aPTT, PT in sec and INR) are within normal limits on the day of the biopsy. The day of biopsy will be moved ahead between Day 8 and Day 11 at a time of Cycle 1 when platelet count has not reach yet the nadir under BI 894999 treatment To avoid the need for switching patients from a vitamin K antagonist treatment or novel oral anticoagulant to low molecular weight heparin for the performance of biopsies, patients under these oral anticoagulation therapies are not requested anymore to undergo tumour biopsies. Clarification of significance of troponin CTCAE grade 3 considered as drug-related: CTCAE grade 3 troponin increases were seen in several patients under BI 894999 without evidence of cardiotoxicity shown from additional cardiac evaluation performed in these patients and without any concomitant signs of myocardial infarction. The real significance of increased troponin in this patient population is not totally understood. For this reason, in patients showing a CTCAE grade 3 troponin increase considered drug-related by the investigator, the drug intake will be interrupted as for any DLT until additional cardiac work-up can rule out emerging cardiotoxicity. In this case, the patient will be allowed to resume the treatment at a reduced dose after a new LVEF evaluation, to be repeated every two cycles thereafter, with instructions in case of significant drop of LVEF.

		For this reason LVEF lower than 50% has been added as an exclusion criterion. Suppression of mandatory bone aspirate and biopsy in DLBCL patients in screening and in case of CR was decided because the main objective of this phase I study is the characterization of the safety and not the efficacy. This will decrease the burden of examinations in DLBCL patients.

11.7 GLOBAL AMENDMENT 7

Number of global amendment		7
Date of CTP revision		05 Sep 2018
EudraCT number		2015-001111-12
BI Trial number		1367.1
BI Investigational Product(s)		BI 894999
Title of protocol		An open label, Phase Ia/Ib dose finding study with BI 894999 orally administered once a day in patients with advanced malignancies, with repeated administration in patients with clinical benefit
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Clinical Trial Protocol Synopsis, footnote 5 of Flow Chart Schedule B first cycle, Abbreviations, 2.1, 2.3, 3.1, 3.3.1, 3.3.2.1, 3.3.3, 3.3.4.1, 4.1.1, 4.1.3.1, 4.1.4.2, 4.1.4.3.1, 4.1.8, 5.3.5.1, 5.3.6.1, 5.5.1.2.2, 7.7, 8, 8.1, 8.2, 8.3.2, 8.4.2, 8.6, 9, 10.6
Description of change		Clinical Trial Protocol Synopsis, footnote 5 of Flow Chart Schedule B first cycle, 2.1, 2.3, 3.1, 3.1.1, 3.3.2.1, 3.3.4.1, 4.1.3, 4.1.4.2, 8.1 - NC cohort will recruit up to 20 patients instead of an estimated number of 5

		patients, increasing the sample size by 15 patients, up to 158 patients in total for the study - NC cohort will allow recruitment of patients ≥ 15 years of age at the time of consent. When patients are aged between 15 and <18 years, they will have to sign an assent form while parents (both or one according to national regulation) or the legal guardian must sign informed consent forms - NC patients may be included even with non-measurable disease - for NC patients, washout for monoclonal antibodies must be discussed with the sponsor - Addition of a DMC meeting once the first and once the second adolescent patient completes Cycle 1 to assess whether the adult dose is tolerable in adolescents - NC patients who are progressing at the end of a cycle but who still have a clinical benefit and no other treatment option available may continue receiving the study treatment as long as they derive benefit. - Addition of reference R18-2451 Sections 3.1, 3.3.4.1, 4.1.4.2, 4.1.4.3.1, 5.3.6.1 - Removal of the maximum treatment break period between two cycles: if a patient requires more than an additional break of 14 days in Schedule B, in addition to the one week off of the schedule, the patient is allowed to start a next cycle. If it is due to a drug related AE, the treatment should be continued at a reduced dose. This is also updated in the DLT definitions for solid tumours and for DLBCL - Removal of the limitation of dose reduction to twice for a single patient Section 2.3 - Explanation on increased troponin levels handling is updated to match the information in the IB - Addition of reference R18-2390 on the

		BET-inhibitor GSK 525762 publication reporting prolonged coagulation times Sections 3.1, 3.1.1 - DMC meetings will happen on regular basis as well during phase Ib (at least once every 3 months) Section 3.3.3 - Radiotherapy given with curative intent is not allowed in the four weeks before the start of trial treatment or during the trial while palliative radiotherapy is allowed without wash out Sections 4.1.8, 8, 8.1, 8.2, 8.3.2, 8.4.2, 8.6 - As the trial will be extended also to the USA to help with the recruitment of NC patients, the specific requirements for USA were added and each time speaking about IEC, it is now referring to IRB / IEC Section 4.2.2.1 and Appendix 10.6 - The list of CYP1A2, CYP 2C8 and CYP 3A4 was updated to clinically relevant substrates. Section5.5.1.2.2: - analyses of the tumour biopsies will include pharmacodynamics changes such as the HEXIM1 modulation and for efficacy will include the analysis of modulation of target genes such as Myc and genes associated with apoptosis
Rationale for change		Extension of NC cohort up to 20 patients and allowance of NC patients ≥ 15 years of age at the time of consent, allowance of NC patients who are progressing under trial treatment to continue with the treatment if they derive clinical benefit and no other treatment option is available: NC is a very aggressive malignancy for which no standard of care has been established. As this rare disease is observed in adolescents and young adults, for this indication, the trial will allow inclusion of minor patients aged 15 years or more. Indeed, the dose, safety and metabolism in adolescents of ≥15 years

		are expected to be similar to adults because body size is expected to be close to adults and organ maturation is expected to be completed. However, to confirm the hypothesis that safety is similar in adolescents and adults, a mandatory DMC meeting will take place after the first and second adolescent patient complete Cycle 1 to assess whether the adult dose is tolerable in adolescents. In this population the benefit is expected to outweigh the risks because there is no standard treatment available and BI 894999 is specifically targeting the NUT-BRD fusion that is characteristic for the disease. The trial will also be extended to the USA to help with the recruitment of NC patients. NC patients will be allowed in the trial even if they have no measurable disease because PFS will also be an important point of efficacy evaluation in addition to RECIST evaluation in this rare and aggressive disease and to give a maximum of NC patients the possibility to participate to the trial when no other treatment option is available. Removal of the maximum treatment break period between two cycles and removal of the limitation of dose reduction to twice for a single patient: this is to avoid that a patient deriving clinical benefit from the drug would have to stop if an AE does not recover within 14 days or that a patient who still has drug related AEs necessitating a further dose reduction after having already had two would need to stop the trial drug while deriving benefit from it. DMC meetings will also be held in an official way in the phase Ib to make sure there is close follow-up on the global safety profile of the drug and decisions on further treatment of the patients in the trial are made by all principal investigators together with the BI trial staff. Clarification of the differentiation between curative and palliative radiotherapy in the exclusion criteria Some additional precision on the intended analyses on tumour tissue from biopsies

11.8 GLOBAL AMENDMENT 8

Date of Amendment		05 Nov 2018
EudraCT number		2015-001111-12
BI Trial number		1367.1
BI Investigational Product(s)		BI 894999
Title of protocol		An open label, Phase Ia/Ib dose finding study with BI 894999 orally administered once a day in patients with advanced malignancies, with repeated administration in patients with clinical benefit
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Clinical Trial Protocol Synopsis, Flow Charts Schedule B first cycle and second and further treatment cycles, 2.3, 3.3.1, 3.3.2, 3.3.3, 4.1.1, 4.1.4.1, 5.1.2, 5.1.3, 5.2.1, 5.3.3, 5.3.6.1, 5.5.1, 5.5.1.2, 7.3.2, 7.3.3.2, 10.5.1, 10.5.2, 10.5.3, 10.5.4
Description of change		Trial synopsis, Sections 5.1.2, 5.1.3, 7.3.2 and 7.3.3.2: - disease control rate is put as a further endpoint and not a secondary endpoint anymore - precision that a minor response according to RECIL 2017 is not included in the evaluation of objective responses Flow Charts for Schedule B, Sections 2.3, 5.3.3, 10.5.1, 10.5.2 and 10.5.3 - Clarification that troponin hs is required each time a safety lab is requested per protocol and that the highly sensitive troponin assay may be a T hs or a I hs assay Section 5.3.3: coagulation parameters - Addition that additional coagulation investigations are to be performed as appropriate when abnormal coagulation parameters are detected in the routine safety laboratory assessments Flow Chart for Schedule B Cycle 1 and Sections 3.3.3.1, 3.3.3.2, 5.3.3 and 10.5.1: - Addition of Hep B, Hep C and HIV testing at screening to exclude active infection

		Flow Charts for Schedule B, Sections 5.2.1, 10.5.1, 10.5.3 and 10.5.4 - Imaging evaluation for tumour assessment at screening and for EOT and FU do not need to be repeated if performed in the last 6 weeks (prior to start of trial treatment at screening) instead of 4 weeks. Section 5.3.6.1 - Addition in the DLT definitions of CTCAE grade≥ 3 thrombocytopenia coupled with grade ≥ 2 of bleeding Section 3.3.2: - Minimal previous standard treatments are added for CRC, SCLC, mCRPC and DLBCL patients Sections 3.3.1, 3.3.2 inclusion criterion 12, 5.5.1, 5.5.1.2 and 10.5.1: - clarification that tumour biopsies are optional for NC patients and not required for patients with therapeutic INR because of treatment with a vitamin K antagonist or a novel oral anticoagulant 4.1.1 and 4.1.4.1: the drug intake is as follows: Once daily intake, in the morning, after an overnight fast, 1 hour before breakfast, to swallow without crushing, with at least 250 mL of water (except for the food interaction cohort.
Rationale for change		These changes are performed further to the review of protocol version 7.0 by the BfArM authorities of Germany and of protocol version 8.0 by the US FDA. The change of request of an overnight fast before drug intake is adapted further to the results from the [redacted] sub-study in phase Ia solid tumours which showed that food intake before drug intake caused approximately 30% decrease in the extent of absorption. There was no or only very limited effect of food on the rate of absorption.

11.9 GLOBAL AMENDMENT 9

Date of Amendment		05 Feb 2019
EudraCT number		2015-001111-12
BI Trial number		1367.1
BI Investigational Product(s)		BI 894999
Title of protocol		An open label, Phase Ia/Ib dose finding study with BI 894999 orally administered once a day in patients with advanced malignancies, with repeated administration in patients with clinical benefit
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Clinical Trial Protocol Synopsis, Flow Charts for Schedules A and B and addition for Schedule C first cycle and second and further treatment cycles, 1.2.1, 1.2.3,1.3, 2.2, 3.1, 3.1.1, 3.2, 3.3.1, 3.3.2.1, 3.3.3.2, 4.1.1, 4.1.2, 4.1.3, 4.1.4, 4.1.6, 4.2.1, 5.1.1, 5.1.2, 5.1.3, 5.2.1, 5.3.6.1, 5.5, 6.1, 6.2, 6.2.1, 7.1, 7.3.1, 7.3.2, 7.3.3.1, 7.3.6, 7.4, 7.7, 8, 8.6, 9.1, 10.2.1, 10.3, 10.4, 10.5
Description of change		Synopsis, Flow Charts for Schedule C first cycle and for second and further cycles, 2.2, 3.1, 3.1.1, 4.1.1, 4.1.2, 4.1.3.1, 4.1.3, 4.1.4, 5.1.1.1, 5.1.2, 5.2.1, 5.3.6.1, 6.1, 6.2, 7.1, 7.3.1, 7.3.2, 7.3.6, 7.4, 7.7, 8, 10.2.1, 10.3.2, 10.4, 10.5: - Addition of a third intermittent schedule, Schedule C, to be tested in Phase Ia, with a loading dose on Day 1 followed by a maintenance dose on the six next days and a week off, repeated every two weeks in 4-week cycles This implies a change in the total number of patients with 18 additional patients foreseen to reach and confirm MTD in Schedule C. Schedule C recruitment will start in Belgium in the two sites participating since the beginning of the study in July 2015 and with priority in these sites to recruitment for Schedule C (with the possibility later on to extend to further Belgian sites if needed) and with priority in these sites to recruitment for Schedule C. When a dose reduction is needed in Schedule C for a single patient, it will happen with a decrease by steps of 1 mg for the loading dose and 0.5 mg for the maintenance dose, each time

		a reduction is necessary, not going lower than 1 mg for the maintenance dose. Synopsis, 1.2.1, 1.3, 2.2, 3.1, 4.1.1, 4.1.2, 4.1.3, 4.1.6, 5.1.3, 6.1, 7.1, 7.4, 10.3.1 - Clarification on what already happened in the trial until this version of the protocol and what still needs to be done for Phase Ia and Phase Ib. What already happened is now put in past tense, what is ongoing is in the present tense and what will happen in the future is in the future tense - Clarification that 0.2 mg, 5 mg and 20 mg tablets strengths are no longer available for the trial 3.3.3.2 - Deletion of request for a stable dose of steroids in the last four weeks prior to study treatment of a DLBCL patient Both Flow Charts for Schedule B, 3.3.1, 5.5.1, 10.5.1, 10.5.2 : - Clarification that the EDTA DNA sample is mandatory when there is tumour tissue obtained from the patient, being it archival tumour tissue or tissue from a fresh tumour biopsy, but only to be taken once in the course of the trial for patients having consented to a fresh tumour biopsy or sending of archival tumour tissue - Clarification that the on treatment biopsy in Phase Ib may remain optional if no easily accessible lesions are available 3.1 - clarification that the patient's overnight hospitalization in Cycle 1 for the periods of intensive PK is left to the discretion of the investigator and based on patient's convenience but is not mandatory 3.3.2.1, criterion 10 c.: - Addition of bevacizumab for patients eligible to this treatment and of an anti-EGFR in RAS wild type metastatic CRC

		3.3.2.2, criterion 1: - Specification of CAR-T cells and other non-listed therapies as part of standard possible treatment, depending on the country where the patient is treated 4.2.1: deletion of the request to register a new anti-cancer treatment after the REP on a separate page of follow-up therapy. 6.2.1: deletion of the request to record the date of progression after previous line(s) of therapy for advanced or metastatic disease.
Rationale for change		- Further to the results from modelling of toxicity observed on thrombocytes and results of PK and pharmacodynamics, an additional dose escalation will be performed with a Schedule C - As the protocol is now ongoing since July 2015 and several changes were brought to the design, it will make the understanding easier for new readers on what was done and what is still ongoing, explaining the DMC decisions until now. - In DLBCL patients in need of a treatment, it is not always possible to wait until they reach a stable dose of corticosteroids for four weeks before treatment as the steroids are used to allow the transition between previous treatment and the trial treatment. - It was unclear in the previous versions of the protocol how many EDTA DNA samples had to be performed for a single patient and when. - For some patients, it may be difficult to obtain a second tumour biopsy a few weeks after the first one if there is no easily accessible lesion and the difficulty to obtain a second biopsy should not prevent patients in need for an experimental treatment from entering the trial - Overnight hospitalization on the intensive PK periods is not mandatory if not deemed necessary by the investigator and/or not deemed more convenient for the patient

		- In sections 3.3.2.1,Criterion 10.c. and section 3.3.2.2, Criterion 1, the clarification on specification of previous treatment is performed further to a request from the French Agency "ANSM" - No record on a specific page of which next line of anti-cancer treatment is given and no record of dates of previous cancer progressions were performed until now and are not necessary in this early stage trial

11.10 GLOBAL AMENDMENT 10

Date of Amendment		24 Sep 2019
EudraCT number		2015-001111-12
BI Trial number		1367.1
BI Investigational Product(s)		BI 894999
Title of protocol		An open label, Phase Ia/Ib dose finding study with BI 894999 orally administered once a day in patients with advanced malignancies, with repeated administration in patients with clinical benefit
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Synopsis, Flow Charts, Abbreviations, 1.3, 2.2, 3.1, 3.1.1, 3.2, 3.3.2 (inclusion criterion 12), 3.3.3.1 (exclusion criteria 13 and 14), 4.1.2, 4.1.4, 4.1.4.2, 4.2.2.1, 5.1.1.1, 5.1.1.2, 5.1.2, 5.1.3, 5.2.1, 5.3.1.1, 6.1, 6.2, 6.2.3.1, 6.2.3.2, 7.1, 7.3, 7.3.1, 7.3.2, 7.3.3.2, 7.7, 8, 8.6, 10.3.2, 10.5
Description of change		Overall change in the whole document: the naming for NUT midline carcinoma is adapted to NUT carcinoma with abbreviation of NC instead of NMC Changes for the NC patients: Synopsis, Flow Charts for Schedules B and C, 1.3, 2.2, 3.1 (design for Phase Ib), 3.1.1, 3.3.2.1, 3.3.3.1, 4.1.2, 4.2.2, 5.1.1.2, 5.2.1, 6.1, 6.2.1, 6.2.3.1, 7.1, 7.3.2, 7.3.3.2, 7.7 - Possibility for DMC to recommend adding a NC cohort treated with Schedule C in Phase Ib once MTD is known in Phase Ia in patients with solid tumours, in order to recommend the schedule and dose for further development in NC patients. If the

		DMC recommends the start of NC cohort with Schedule C, the Schedule B NC cohort will then be closed to recruitment. If the DMC recommends Schedule B, recruitment of NC patients will continue with Schedule B and Schedule C NC cohort will not open - Total number of patients is estimated to up to 196 with an addition of up to 40 patients in Schedule C NC cohort and up to 40 patients in Schedule B NC cohort if Schedule C NC cohort is not opened to recruitment - Addition of overall survival (OS) as secondary endpoint for the NC patients who consented to collect this information - Addition of overall clinical benefit as judged by investigator and of time to treatment failure for the NC patients in the further endpoints - Germany will now also participate to the recruitment of patients aged between 15 and <18 years with MRI used for the imaging assessments (no CT scans for the trial imaging assessments in this adolescent population) - NC patients do not need to have a progressive disease shown by RECIST 1.1 in the past 6 months (inclusion criterion 12) - Other investigational or marketed anti-cancer treatments are not allowed in the previous two weeks or five times the half-life of the drug for NC patients (exclusion criteria 13 and 14) - For NC patients, allowance to perform palliative radiotherapy on target lesions as well as on non-target and to lesions indicating progressive disease for patients who are deriving clinical benefit from the study treatment - Addition to the data of the collection of the methodology used to diagnose NC, of the NUT fusion partner and of the threshold for a positive NC - Possibility of addition of a fifth cohort in Phase Ib in the statistical model: NC cohort treated with Schedule C

		Synopsis, Flow Charts for Schedule C, 1.3, 2.2, 3.1, 3.1.1, 3.2, 4.1.2, 4.1.4, 4.1.4.2, 5.1.1.1, 5.1.2, 6.1, 7.1, 7.3.1, 7.3.2, 7.7, 10.5 - The MTD will also be determined for Schedule C in patients with DLBCL and once both MTD in Schedules B and C are known for this patient population, the DMC will recommend the best Schedule to select between B and C to further extend the MTD cohort - In the first cohort of DLBCL patients treated with Schedule C, the loading dose will be 4 mg and the maintenance dose 2 mg - For the determination of the MTD in Schedule B in DLBCL, a total of 12 DLBCL patients treated with Schedule B will be sufficient mCRPC and CRC cohorts of expansion Phase Ib with Schedule B were closed for futility. Flow Charts Schedule A: the missing cross for the collection of body weight at the FU visit was added. RDC and Electronic Data Capture (EDC) mentioned as data capture systems
Rationale for change		Changes for the NC patients: Synopsis, Flow Charts for Schedules B and C, 1.3, 2.2, 3.1 (design for Phase Ib), 3.1.1, 3.3.2.1, 3.3.3.1, 4.1.2, 4.2.2, 5.1.1.2, 6.1, 6.2.1, 6.2.3.1, 7.1, 7.3.2, 7.3.3.2, 7.7 - If Schedule C appears to have a better tolerability profile than Schedule B in patients with solid tumours, NC patients may also better benefit from Schedule C and have a better treatment coverage without interruptions due to toxicity such as thrombocytopenia. - At the present time there is no recognized standard treatment for NC patients. The number of patients in this trial is extended for NC patients, being it in cohort of Schedule B or in cohort with Schedule C if Schedule C appears better, to make it

		possible for patients to have the possibility to join a trial until opening of other trials in this indication. - Because NC patients may be entered in the trial without target lesions, there is a need to be able to evaluate the efficacy with other criteria than the RECIST 1.1 imaging. This is the reason for adding overall survival for NC patients. Also because patients may continue beyond progression if they derive clinical benefit, time to treatment failure was added to the PFS. Overall clinical benefit judged by the investigator is an indirect way of adding the quality of life dimension in this very ill patient population - Germany further evaluated the possibility of including adolescent patients without the radiation burden of imaging by CT scan. They agreed to include adolescent patients aged between 15 and < 18 at the condition that these patients would not undergo CT scans but only MRI imaging evaluations. In other countries, the choice of CT or MRI is left to the investigator for all patients but the same method is to be used along the study for a single patient - Inclusion criterion 12 of section 3.3.2: As there is no established effective treatment for NC patients, a newly diagnosed NC patient can be included in the study if the investigator considers that the patient has no other treatment options. - Exclusion criteria 13 and 14: because NC patients are usually progressing fast and cannot afford long wash-out periods without treatment, the maximum wash-out duration for drug with longer half-lifes was reduced to 2 weeks instead of 4. - Section 4.2.2.1: amendment introduced in order to allow NC patients who have a mixed radiological response to the study treatment to remain on treatment if the investigator considers that the patient is deriving clinical benefit. Lesions that are irradiated will not be considered evaluable as per RECIST 1.1

		- Recording of additional characteristics of the NC diagnosis should help better defining the patient population deriving the most benefit from the BI 894999 treatment The addition of MTD determination of Schedule C in a DLBCL patient population is aimed to try and overcome the toxicity mainly thrombocytopenia grade 4 seen with Schedule B higher doses and to be able to increase the total dose given to these patients with less interruptions due to toxicity. Flow Charts of Schedule A: addition of missing crosses for body weight at FU to correct an omission in previous versions of the protocol Electronic Data Capture (EDC) mentioned as data capture system in addition to RDC because BI will transition the trial from an actual RDC system to an EDC system during the month of September 2019.

11.11 GLOBAL AMENDMENT 11

Date of Amendment		24 Jun 2020
EudraCT number		2015-001111-12
BI Trial number		1367.1
BI Investigational Product(s)		BI 894999
Title of protocol		An open label, Phase Ia/Ib dose finding study with BI 894999 orally administered once a day in patients with advanced malignancies, with repeated administration in patients with clinical benefit
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Synopsis, Flow Charts, 1.3, 2.2, 2.3, 3.1, 3.3.2.1, 3.3.3, 4.1.2, 4.1.4, 4.1.4.1, 4.1.4.2, 4.1.4.3.1, 5.3.4, 5.4.2.2, 5.5.1.1, 6.1, 6.2, 7.7, 10.2.1: 3, 10.2.1: 4, 10.5.2, 10.5.3
Description of change		Synopsis: - increase of the number of participating countries up to 10 Synopsis and Section 7.7: - adaptation of the sample size to reflect actual number of patients already treated

		and planned ones still to be recruited Sections 2.3, 3.3.3, 3.3.4.1, 4.1.4, 4.1.4.3.1: - Section 2.3: statement of evaluation of the benefit-risk in relation to the COVID-19 pandemic - Section 3.3: exclusion of active or recent infection within previous 6 weeks with SARS-CoV-2 - Section 3.3.4.1: withdrawal of a patient who would have a COVID-19 infection confirmed a PCR test during his participation to the trial and for whom the benefit-risk balance would not be in favour of resuming treatment after recovery - Section 4.1.4: possibility for the investigator to judge the benefit-risk balance for a patient's safety to continue trial treatment but to restrict site visits and perform safety assessments via local tests and phone visits with the patients during COVID-19 pandemic - Section 4.1.4.3.1: interruption of BI 894999 treatment in case of COVID-19 infection until recovery and then decision by Investigator and Sponsor if treatment may be resumed or not according to benefit-risk balance Changes for the NC and DLBCL patients from Schedule C starting from protocol version 12.0 onwards: - addition of specific Flow Charts for Cycle 1 and further Cycles - Sections 4.1.4.1 and 10.5.2: suppression of Day 2 part of the visit 1 and for the need to keep patients after 4h post-dose on Day 1 in Cycle 1 - Flow Chart for Schedule C DLBCL and NC patients and Section 10.5.2; possibility to perform Cycle 1 Visit 2 of Day 8 locally with a remote phone call visit by the Investigator, if allowed by local regulations - Sections 6.2 and addition of 10.2.1: 4: decrease in the number of PK blood samples with suppression of PK on Day 15

		of Cycle 1 - Sections 5.5.1.1 and 10.2.1: 4: decrease in the number of pre-specified PGx blood samples for patients recruited under protocol version 12.0 - Section 6.1: possibility for a patient unable or unwilling to attend a clinic visit to have the evaluation performed by a remote visit if deemed safe by the Investigator, after agreement with the Sponsor, if allowed by local regulations - Section 4.1.4.2: after Cycle 1, the tests of Day 15 visit may be performed locally with a phone call visit with the investigator to discuss results and safety with the patient, if allowed by local regulations - Section 4.1.4.2: starting from Cycle 6 onwards, tests of Visit 1 of even Cycles may be performed locally followed by a phone call visit with the Investigator, if allowed by local regulations - Section 4.1.4.2: if deemed safe by the Investigator to have Visit 1 of even cycles performed locally with a phone call visit, medication dispensation may happen for two cycles at uneven cycles, starting from Cycle 5 or a direct shipment from site to patient may happen provided that the shipment occurs with a courier approved by the Sponsor in order to ensure correct conditions of shipments, if allowed by country regulations. - Flow Charts for Schedule C NC and DLBCL patients, Sections 5.3.4, 10.5.2: ECGs should be performed in triplicate for central reading by CRO but this is not always possible for the sites. So, the recommendation is to perform it in digitalized way and in triplicate whenever possible but if not, when patient is on site, it should be digitalized with ECG device provided by the central reading CRO and if not done on site, the original tracing must be provided to the central reading CRO for assessment.

		Flow Chart for Schedule C: specification of the Flow Charts for Solid Tumour Patients from Phase Ia for whom no changes except the suppression of the urine collection for PK. Sections 5.4.2.2 and 10.2.1: 3: suppression of urine collection for PK fo all patients starting with protocol version 12.0 Sections 1.3, 2.2, 3.1, 3.1.1, 4.1.2, 6.1: update of the actual situation of the trial at the time of the protocol version 12.0 with MTD determined for Schedule C in DLBCL patients, the opening of Schedule C in DLBCL patients, the MTD determination of Schedule C in patients with solid tumours and the decision of DMC to open the NC cohort to Schedule C while closing the Schedule B cohort. These updates are also reflected in the use of past tense for parts of the study already finished at this stage of protocol revision. Section 3.3.2.1: inclusion criterion 2: in Germany and in South Korea, only legally adult patients may be included in the trial.
Rationale for change		The COVID-19 pandemic requires adaptations to the benefit-risk evaluation for ongoing and new patients in the trial with additional guidance to ensure patient's safety by decreasing in-patients visits to the sites if needed and by giving instructions in case a patient is tested positive to SARS-CoV-2. Changes for the DLBCL and NC patients of Schedule C: decrease in the number of visits and in the number of PK and biomarkers samples is done to lighten the burden of the trial for these heavily ill patients. The allowance for some visits to be performed remotely by the investigator for these patients after all tests having been done locally is also to decrease the number of travels to the minimum acceptable according to the individual benefit-risk evaluation as judged by the Investigator in the post-COVID-19 situation with possible travel restrictions. For the same reason, the protocol version 12.0 allows the possibility to dispense the drug for two consecutive cycles starting from Cycle 5 onwards if the patient is tolerating the drug well or to have a direct shipment

		from site to patient in secured acceptable shipment conditions, if allowed by the country regulations. Stop of urine collection for PK because the urine PK profile of the drug is enough characterized with the already collected samples.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	25 Jun 2020 09:54 CEST
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Approval-Therapeutic Area [redacted]		25 Jun 2020 14:26 CEST
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Meaning of Signature	**Signed by**	**Date Signed**